

WEBVTT

NOTE duration:"00:51:53.320000"

NOTE recognizability:0.833

NOTE language:en-us

NOTE Confidence: 0.9624003575

00:00:00.000 --> 00:00:02.000 I think we can start to get in.

NOTE Confidence: 0.9624003575

00:00:02.000 --> 00:00:04.526 It's wonderful to be here this

NOTE Confidence: 0.9624003575

00:00:04.526 --> 00:00:06.786 morning and to introduce somebody

NOTE Confidence: 0.9624003575

00:00:06.786 --> 00:00:09.271 who is absolutely exceptional and

NOTE Confidence: 0.9624003575

00:00:09.271 --> 00:00:12.170 who is newly recruited to our

NOTE Confidence: 0.9624003575

00:00:12.170 --> 00:00:14.235 department in neurosurgery and also

NOTE Confidence: 0.9624003575

00:00:14.235 --> 00:00:16.362 to Smilo in the Cancer Center.

NOTE Confidence: 0.9624003575

00:00:16.362 --> 00:00:18.126 Dr. Rol Vierhok is Professor in

NOTE Confidence: 0.9624003575

00:00:18.126 --> 00:00:19.531 the Department of Neurosurgery

NOTE Confidence: 0.9624003575

00:00:19.531 --> 00:00:21.637 at the Yale School of Medicine.

NOTE Confidence: 0.9624003575

00:00:21.640 --> 00:00:23.705 Following graduation with a PhD

NOTE Confidence: 0.9624003575

00:00:23.705 --> 00:00:25.770 in Medicine from their Aerosmiths

NOTE Confidence: 0.9624003575

00:00:25.839 --> 00:00:28.319 University Medical Center in Rotterdam,

NOTE Confidence: 0.9624003575

00:00:28.320 --> 00:00:30.645 the Netherlands Role joined the
NOTE Confidence: 0.9624003575

00:00:30.645 --> 00:00:32.970 Broad Institute Dana Farber Cancer
NOTE Confidence: 0.9624003575

00:00:33.042 --> 00:00:35.717 Institute as a postdoctoral associate,
NOTE Confidence: 0.9624003575

00:00:35.720 --> 00:00:38.639 supported by a fellowship from the Dutch
NOTE Confidence: 0.9624003575

00:00:38.639 --> 00:00:40.716 Cancer Society during the time at the Broad,
NOTE Confidence: 0.9624003575

00:00:40.720 --> 00:00:42.400 he was part of the team
NOTE Confidence: 0.9624003575

00:00:42.400 --> 00:00:43.880 analyzing data from the TCGA.
NOTE Confidence: 0.9624003575

00:00:43.880 --> 00:00:46.785 He led the Identification and
NOTE Confidence: 0.9624003575

00:00:46.785 --> 00:00:49.109 Characterization of Gene Expression
NOTE Confidence: 0.9624003575

00:00:49.109 --> 00:00:51.207 subtypes and glioblastoma work
NOTE Confidence: 0.9624003575

00:00:51.207 --> 00:00:54.081 that resulted in a Seminole Cancer
NOTE Confidence: 0.9624003575

00:00:54.081 --> 00:00:56.464 Cell 2010 publication will move
NOTE Confidence: 0.9624003575

00:00:56.464 --> 00:00:59.320 to MD Anderson Cancer Center in
NOTE Confidence: 0.9624003575

00:00:59.408 --> 00:01:02.120 2010 to start his own laboratory.
NOTE Confidence: 0.9624003575

00:01:02.120 --> 00:01:02.898 Since then,
NOTE Confidence: 0.9624003575

00:01:02.898 --> 00:01:05.232 the Veerhawk lab has studied tumor

NOTE Confidence: 0.9624003575

00:01:05.232 --> 00:01:07.299 evolution and mechanisms of therapy

NOTE Confidence: 0.9624003575

00:01:07.299 --> 00:01:10.155 resistance in low and high grade gliomas.

NOTE Confidence: 0.9624003575

00:01:10.160 --> 00:01:11.828 The group was foundational

NOTE Confidence: 0.9624003575

00:01:11.828 --> 00:01:13.496 in establishing the Glioma

NOTE Confidence: 0.9624003575

00:01:13.496 --> 00:01:15.000 Longitudinal Analysis Consortium,

NOTE Confidence: 0.9624003575

00:01:15.000 --> 00:01:17.526 which has established a resource of

NOTE Confidence: 0.9624003575

00:01:17.526 --> 00:01:19.967 molecular profiles over time on a

NOTE Confidence: 0.9624003575

00:01:19.967 --> 00:01:22.037 large cohort of patients with glioma.

NOTE Confidence: 0.9624003575

00:01:22.040 --> 00:01:24.475 They identified and described genetic

NOTE Confidence: 0.9624003575

00:01:24.475 --> 00:01:26.423 scars and cellular phenotypes

NOTE Confidence: 0.9624003575

00:01:26.423 --> 00:01:28.448 associated with glioma progression

NOTE Confidence: 0.9624003575

00:01:28.448 --> 00:01:29.915 and disease recurrence.

NOTE Confidence: 0.9624003575

00:01:29.920 --> 00:01:32.115 Extra chromosomal DNA amplifications were

NOTE Confidence: 0.9624003575

00:01:32.115 --> 00:01:34.657 discovered as critical drivers and are

NOTE Confidence: 0.9624003575

00:01:34.657 --> 00:01:36.913 now a major part of the team's research.

NOTE Confidence: 0.9624003575

00:01:36.920 --> 00:01:38.584 After being affiliated with
NOTE Confidence: 0.9624003575

00:01:38.584 --> 00:01:40.248 the Jackson Jackson Laboratory
NOTE Confidence: 0.9624003575

00:01:40.248 --> 00:01:42.159 for Genomic Medicine in 2016.
NOTE Confidence: 0.9624003575

00:01:42.160 --> 00:01:45.310 I can tell you our department leadership
NOTE Confidence: 0.9624003575

00:01:45.310 --> 00:01:47.810 fought very hard to recruit him
NOTE Confidence: 0.9624003575

00:01:47.810 --> 00:01:50.536 here to Yale and he joined us in the
NOTE Confidence: 0.9624003575

00:01:50.536 --> 00:01:52.080 Department of Neurosurgery in 2023.
NOTE Confidence: 0.9624003575

00:01:52.080 --> 00:01:54.720 Roll is a recipient of the
NOTE Confidence: 0.9624003575

00:01:54.720 --> 00:01:56.100 AAAS Watchal Award,
NOTE Confidence: 0.9624003575

00:01:56.100 --> 00:01:58.860 the Agilent the Early Career Professor
NOTE Confidence: 0.9624003575

00:01:58.860 --> 00:02:01.920 Award and the Peter Stack Memorial Award.
NOTE Confidence: 0.9624003575

00:02:01.920 --> 00:02:04.636 He's also Co founder of Boundless Bio.
NOTE Confidence: 0.9624003575

00:02:04.640 --> 00:02:06.250 I can tell you in the short time that I've
NOTE Confidence: 0.9624003575

00:02:06.296 --> 00:02:07.759 had the privilege of working with him,
NOTE Confidence: 0.9624003575

00:02:07.760 --> 00:02:10.304 he's truly exceptional and I'm really
NOTE Confidence: 0.9624003575

00:02:10.304 --> 00:02:12.920 excited for this talk and for all

NOTE Confidence: 0.9624003575

00:02:12.920 --> 00:02:15.320 of the work that we have to come.

NOTE Confidence: 0.9624003575

00:02:15.320 --> 00:02:16.584 So without further ado,

NOTE Confidence: 0.9624003575

00:02:16.584 --> 00:02:18.480 thank you so much Doctor Veerhark.

NOTE Confidence: 0.807504614285714

00:02:19.920 --> 00:02:20.674 Thanks Jennifer.

NOTE Confidence: 0.807504614285714

00:02:20.674 --> 00:02:22.559 That very, very kind introduction.

NOTE Confidence: 0.807504614285714

00:02:22.560 --> 00:02:25.365 And so I joined the Department

NOTE Confidence: 0.807504614285714

00:02:25.365 --> 00:02:28.515 of Neurosurgery in April of last

NOTE Confidence: 0.807504614285714

00:02:28.515 --> 00:02:30.200 year after some discussions with

NOTE Confidence: 0.807504614285714

00:02:30.200 --> 00:02:31.360 Doctor Grinnell and others.

NOTE Confidence: 0.807504614285714

00:02:31.360 --> 00:02:33.480 And to be honest, it wasn't that hard.

NOTE Confidence: 0.807504614285714

00:02:33.480 --> 00:02:35.124 I was pretty convinced very quickly

NOTE Confidence: 0.807504614285714

00:02:35.124 --> 00:02:37.270 that this was going to be a great

NOTE Confidence: 0.807504614285714

00:02:37.270 --> 00:02:38.515 place to continue our research.

NOTE Confidence: 0.807504614285714

00:02:38.520 --> 00:02:40.445 As we were thinking about

NOTE Confidence: 0.807504614285714

00:02:40.445 --> 00:02:41.600 becoming more translational,

NOTE Confidence: 0.807504614285714

00:02:41.600 --> 00:02:43.424 it was we felt that we that being
NOTE Confidence: 0.807504614285714

00:02:43.424 --> 00:02:45.452 in a clinical environment would we
NOTE Confidence: 0.807504614285714

00:02:45.452 --> 00:02:47.720 greatly benefit our work and what
NOTE Confidence: 0.807504614285714

00:02:47.720 --> 00:02:49.608 what grader clinical environment
NOTE Confidence: 0.807504614285714

00:02:49.608 --> 00:02:51.830 and Yale School of Medicine and
NOTE Confidence: 0.807504614285714

00:02:51.830 --> 00:02:52.880 department of Neurosurgery.
NOTE Confidence: 0.807504614285714

00:02:52.880 --> 00:02:56.093 So I'm a Co founder of a biotech that
NOTE Confidence: 0.807504614285714

00:02:56.093 --> 00:02:59.038 won't be discussing that work today.
NOTE Confidence: 0.807504614285714

00:02:59.040 --> 00:03:00.755 I am also a consultant for neurotrials.
NOTE Confidence: 0.90473884

00:03:03.200 --> 00:03:07.370 So gliomas are the most common
NOTE Confidence: 0.90473884

00:03:07.370 --> 00:03:10.647 molecular tumor type in an in adult
NOTE Confidence: 0.90473884

00:03:10.647 --> 00:03:12.640 patients and the most devastating ones.
NOTE Confidence: 0.90473884

00:03:12.640 --> 00:03:14.550 They're characterized by an infiltrative
NOTE Confidence: 0.90473884

00:03:14.550 --> 00:03:16.078 growth into the environment,
NOTE Confidence: 0.90473884

00:03:16.080 --> 00:03:17.058 into the parencoa,
NOTE Confidence: 0.90473884

00:03:17.058 --> 00:03:18.688 and this makes these tumors

NOTE Confidence: 0.90473884

00:03:18.688 --> 00:03:20.078 exceptionally hard to treat because

NOTE Confidence: 0.90473884

00:03:20.078 --> 00:03:21.990 she can't go in with a knife and

NOTE Confidence: 0.90473884

00:03:21.990 --> 00:03:23.646 cut out the entire the entire

NOTE Confidence: 0.90473884

00:03:23.646 --> 00:03:25.000 structure for obvious reasons.

NOTE Confidence: 0.811431153076923

00:03:27.320 --> 00:03:29.364 Nowadays we recognize traditionally

NOTE Confidence: 0.811431153076923

00:03:29.364 --> 00:03:31.919 we would classify gliomas in

NOTE Confidence: 0.811431153076923

00:03:31.919 --> 00:03:34.478 adult patients by histopathology.

NOTE Confidence: 0.811431153076923

00:03:34.480 --> 00:03:36.365 Fortunately, we've gotten away from

NOTE Confidence: 0.811431153076923

00:03:36.365 --> 00:03:39.063 that as molecular markers do much more

NOTE Confidence: 0.811431153076923

00:03:39.063 --> 00:03:41.313 precise job in doing such classification.

NOTE Confidence: 0.811431153076923

00:03:41.320 --> 00:03:43.760 Nowadays we recognize gliomas based

NOTE Confidence: 0.811431153076923

00:03:43.760 --> 00:03:46.200 on two critical molecular markers.

NOTE Confidence: 0.811431153076923

00:03:46.200 --> 00:03:48.776 1st, we set, we identified the presence

NOTE Confidence: 0.811431153076923

00:03:48.776 --> 00:03:51.891 of absence of a mutation in IDH one

NOTE Confidence: 0.811431153076923

00:03:51.891 --> 00:03:53.831 or IDH 2 isocitrate dehydrogenate.

NOTE Confidence: 0.811431153076923

00:03:53.840 --> 00:03:55.681 And for those cases that carry an
NOTE Confidence: 0.811431153076923

00:03:55.681 --> 00:03:57.678 IDH 1 mutation or an IDH 2 mutation,
NOTE Confidence: 0.811431153076923

00:03:57.680 --> 00:03:59.934 we further separate them by the presence
NOTE Confidence: 0.811431153076923

00:03:59.934 --> 00:04:02.313 of our absence of 1P19Q code deletion.
NOTE Confidence: 0.811431153076923

00:04:02.313 --> 00:04:06.480 So from some arm loss of 1P and 19 Q 19 Q.
NOTE Confidence: 0.811431153076923

00:04:06.480 --> 00:04:08.100 Predominantly the cases that
NOTE Confidence: 0.811431153076923

00:04:08.100 --> 00:04:09.720 have this code deletion,
NOTE Confidence: 0.811431153076923

00:04:09.720 --> 00:04:13.073 we call them code deletions are a majority
NOTE Confidence: 0.811431153076923

00:04:13.073 --> 00:04:15.462 isopathologically all it goes non code
NOTE Confidence: 0.811431153076923

00:04:15.462 --> 00:04:17.630 L So those cases that are IDH mutated
NOTE Confidence: 0.811431153076923

00:04:17.697 --> 00:04:19.893 but don't have that code deletion
NOTE Confidence: 0.811431153076923

00:04:19.893 --> 00:04:22.040 are in majority astrocytomas and the
NOTE Confidence: 0.811431153076923

00:04:22.040 --> 00:04:24.420 IDH wild type cases are mostly the
NOTE Confidence: 0.811431153076923

00:04:24.420 --> 00:04:26.860 glioblastomas and the patients survival
NOTE Confidence: 0.811431153076923

00:04:26.860 --> 00:04:29.166 patterns are according meaning that
NOTE Confidence: 0.811431153076923

00:04:29.166 --> 00:04:31.707 those cases that have no IDH mutation

NOTE Confidence: 0.811431153076923

00:04:31.707 --> 00:04:35.240 do particularly poorly clinically.

NOTE Confidence: 0.811431153076923

00:04:35.240 --> 00:04:37.672 That's not to say that any of these

NOTE Confidence: 0.811431153076923

00:04:37.672 --> 00:04:39.228 tuber types are better to have

NOTE Confidence: 0.811431153076923

00:04:39.228 --> 00:04:41.177 quote UN quote this as far as you

NOTE Confidence: 0.811431153076923

00:04:41.177 --> 00:04:42.599 can ever better have a tumor.

NOTE Confidence: 0.811431153076923

00:04:42.600 --> 00:04:46.310 Patients that are that carry the IDH

NOTE Confidence: 0.811431153076923

00:04:46.310 --> 00:04:49.240 mutant non CODEL tumors are typically

NOTE Confidence: 0.811431153076923

00:04:49.240 --> 00:04:51.800 diagnosed between 35 and 44 years of age,

NOTE Confidence: 0.811431153076923

00:04:51.800 --> 00:04:54.120 so very young in life.

NOTE Confidence: 0.811431153076923

00:04:54.120 --> 00:04:55.624 The codel patient typically

NOTE Confidence: 0.811431153076923

00:04:55.624 --> 00:04:57.880 is around 45 years of age.

NOTE Confidence: 0.811431153076923

00:04:57.880 --> 00:04:59.878 So again relatively early in life.

NOTE Confidence: 0.811431153076923

00:04:59.880 --> 00:05:01.896 So those patients might have much

NOTE Confidence: 0.811431153076923

00:05:01.896 --> 00:05:03.634 better outcomes but they'll mostly

NOTE Confidence: 0.811431153076923

00:05:03.634 --> 00:05:05.620 the majority will still succumb to

NOTE Confidence: 0.811431153076923

00:05:05.620 --> 00:05:07.465 disease even prior to the median
NOTE Confidence: 0.811431153076923

00:05:07.465 --> 00:05:09.055 age of diagnosis for IDH wild
NOTE Confidence: 0.811431153076923

00:05:09.055 --> 00:05:10.840 type tumors which is around 60.
NOTE Confidence: 0.811431153076923

00:05:10.840 --> 00:05:12.520 So these are all bad tumors.
NOTE Confidence: 0.95073869

00:05:15.400 --> 00:05:18.960 Here's the motivation for classifying
NOTE Confidence: 0.95073869

00:05:18.960 --> 00:05:21.756 gliomas by these two molecular markers.
NOTE Confidence: 0.95073869

00:05:21.760 --> 00:05:23.248 And in part it's of course
NOTE Confidence: 0.95073869

00:05:23.248 --> 00:05:23.992 it's clinically it's,
NOTE Confidence: 0.95073869

00:05:24.000 --> 00:05:25.518 it's the survival outcomes as I
NOTE Confidence: 0.95073869

00:05:25.518 --> 00:05:27.359 showed you on the previous slide.
NOTE Confidence: 0.95073869

00:05:27.360 --> 00:05:29.580 But here in this paper
NOTE Confidence: 0.95073869

00:05:29.580 --> 00:05:31.805 from the TCGA from 2015,
NOTE Confidence: 0.95073869

00:05:31.805 --> 00:05:34.475 we demonstrated that not only behave
NOTE Confidence: 0.95073869

00:05:34.475 --> 00:05:36.548 these tumors differently and respond,
NOTE Confidence: 0.95073869

00:05:36.548 --> 00:05:39.356 they they respond different to treatments,
NOTE Confidence: 0.95073869

00:05:39.360 --> 00:05:40.976 but they're really biologically

NOTE Confidence: 0.95073869
00:05:40.976 --> 00:05:42.996 different entities as reflected in
NOTE Confidence: 0.95073869
00:05:42.996 --> 00:05:45.680 the sets of molecular alterations
NOTE Confidence: 0.95073869
00:05:45.680 --> 00:05:47.960 that are commonly detected.
NOTE Confidence: 0.95073869
00:05:47.960 --> 00:05:48.640 For example,
NOTE Confidence: 0.95073869
00:05:48.640 --> 00:05:52.140 in the codon group we find that they
NOTE Confidence: 0.95073869
00:05:52.140 --> 00:05:54.280 are nearly universally carrying
NOTE Confidence: 0.95073869
00:05:54.280 --> 00:05:57.120 mutations in the Turk promoter,
NOTE Confidence: 0.95073869
00:05:57.120 --> 00:05:59.706 as well as relatively spurious mutations
NOTE Confidence: 0.95073869
00:05:59.706 --> 00:06:04.360 in genes like Notch One and NCIC.
NOTE Confidence: 0.95073869
00:06:04.360 --> 00:06:05.332 The non codons,
NOTE Confidence: 0.95073869
00:06:05.332 --> 00:06:07.276 even though they are IDH mutated,
NOTE Confidence: 0.95073869
00:06:07.280 --> 00:06:10.840 rarely contain Turk promoter mutations
NOTE Confidence: 0.95073869
00:06:10.840 --> 00:06:13.670 but are universally mutated in P53 and
NOTE Confidence: 0.95073869
00:06:13.670 --> 00:06:16.760 75% carry hairy alterations in ATRX.
NOTE Confidence: 0.95073869
00:06:16.760 --> 00:06:19.292 So very similar tumor types but
NOTE Confidence: 0.95073869

00:06:19.292 --> 00:06:20.558 molecularly quite different.
NOTE Confidence: 0.95073869

00:06:20.560 --> 00:06:24.440 And then finally IDH wild type tumors
NOTE Confidence: 0.95073869

00:06:24.440 --> 00:06:27.655 again 80% are turb promoter mutated and
NOTE Confidence: 0.95073869

00:06:27.655 --> 00:06:30.520 they are then a majority containing
NOTE Confidence: 0.95073869

00:06:30.520 --> 00:06:33.044 mutations in genes like e.g., FRC DK,
NOTE Confidence: 0.95073869

00:06:33.044 --> 00:06:35.158 N2AP10 and so on and so forth.
NOTE Confidence: 0.95073869

00:06:35.160 --> 00:06:37.210 So biological not just responding
NOTE Confidence: 0.95073869

00:06:37.210 --> 00:06:38.440 differently to treatment,
NOTE Confidence: 0.95073869

00:06:38.440 --> 00:06:40.174 not just different at in terms
NOTE Confidence: 0.95073869

00:06:40.174 --> 00:06:42.399 of at when they present in life,
NOTE Confidence: 0.95073869

00:06:42.400 --> 00:06:44.120 but biologically also quite different.
NOTE Confidence: 0.933013848888889

00:06:46.560 --> 00:06:51.000 Now after we were able to refine the
NOTE Confidence: 0.933013848888889

00:06:51.000 --> 00:06:53.720 classification of gliomas in adult patients,
NOTE Confidence: 0.933013848888889

00:06:53.720 --> 00:06:55.136 a major next a major challenge
NOTE Confidence: 0.933013848888889

00:06:55.136 --> 00:06:56.627 continues to be how these tumors
NOTE Confidence: 0.933013848888889

00:06:56.627 --> 00:06:58.377 respond to treatment and the lack of

NOTE Confidence: 0.933013848888889
00:06:58.377 --> 00:07:00.280 new treatments coming into the clinic.
NOTE Confidence: 0.872608682857143
00:07:02.800 --> 00:07:04.504 Now tumors initiate from a cell
NOTE Confidence: 0.872608682857143
00:07:04.504 --> 00:07:06.623 of origin and over time as these
NOTE Confidence: 0.872608682857143
00:07:06.623 --> 00:07:07.851 cells respond to challenges
NOTE Confidence: 0.872608682857143
00:07:07.851 --> 00:07:09.800 in the tumor microenvironment,
NOTE Confidence: 0.872608682857143
00:07:09.800 --> 00:07:11.680 for example presence of oxygen,
NOTE Confidence: 0.872608682857143
00:07:11.680 --> 00:07:14.080 lack of nutrients and so forth,
NOTE Confidence: 0.872608682857143
00:07:14.080 --> 00:07:15.960 you'll find that intratumoral
NOTE Confidence: 0.872608682857143
00:07:15.960 --> 00:07:17.840 heterogeneity starts to develop.
NOTE Confidence: 0.872608682857143
00:07:17.840 --> 00:07:19.898 And this is a consequence of
NOTE Confidence: 0.872608682857143
00:07:19.898 --> 00:07:21.270 these evolutionary processes and
NOTE Confidence: 0.872608682857143
00:07:21.328 --> 00:07:22.928 clonal selection where some cells
NOTE Confidence: 0.872608682857143
00:07:22.928 --> 00:07:24.984 are better able to deal with
NOTE Confidence: 0.872608682857143
00:07:24.984 --> 00:07:26.556 these limitations than others.
NOTE Confidence: 0.872608682857143
00:07:26.560 --> 00:07:29.690 Therefore they become they they
NOTE Confidence: 0.872608682857143

00:07:29.690 --> 00:07:31.244 they show clonal outgrowth.
NOTE Confidence: 0.872608682857143

00:07:31.244 --> 00:07:33.400 So at the time of diagnosis we're
NOTE Confidence: 0.872608682857143

00:07:33.458 --> 00:07:35.534 dealing with an with an heterogeneous
NOTE Confidence: 0.872608682857143

00:07:35.534 --> 00:07:37.608 tumor with different sets of tumor
NOTE Confidence: 0.872608682857143

00:07:37.608 --> 00:07:39.486 cells marked by specific and mutations
NOTE Confidence: 0.872608682857143

00:07:39.486 --> 00:07:42.960 and other kinds of gene alterations.
NOTE Confidence: 0.872608682857143

00:07:42.960 --> 00:07:44.860 Now critically this process doesn't
NOTE Confidence: 0.872608682857143

00:07:44.860 --> 00:07:47.586 end a diagnosis of course we impose
NOTE Confidence: 0.872608682857143

00:07:47.586 --> 00:07:49.238 treatments onto these tumors.
NOTE Confidence: 0.872608682857143

00:07:49.240 --> 00:07:52.170 You know surgery initially debulking
NOTE Confidence: 0.872608682857143

00:07:52.170 --> 00:07:54.616 surgery combined with radiation and
NOTE Confidence: 0.872608682857143

00:07:54.616 --> 00:07:56.936 chemotherapy which for gliomas in
NOTE Confidence: 0.872608682857143

00:07:56.936 --> 00:08:01.000 majority is stemozolamide, stemozolamide.
NOTE Confidence: 0.872608682857143

00:08:01.000 --> 00:08:03.580 And of course these treatments
NOTE Confidence: 0.872608682857143

00:08:03.580 --> 00:08:06.160 continue to impose these bottlenecks
NOTE Confidence: 0.872608682857143

00:08:06.241 --> 00:08:08.580 onto the tumor and those cells

NOTE Confidence: 0.872608682857143

00:08:08.580 --> 00:08:10.977 best able to deal with radiation,

NOTE Confidence: 0.872608682857143

00:08:10.977 --> 00:08:12.759 best able to deal with chemotherapy

NOTE Confidence: 0.872608682857143

00:08:12.759 --> 00:08:15.000 are the ones that are going to fuel

NOTE Confidence: 0.872608682857143

00:08:15.000 --> 00:08:17.800 the outgrowth and the tumor recurrence.

NOTE Confidence: 0.872608682857143

00:08:17.800 --> 00:08:19.116 So we felt that this would be,

NOTE Confidence: 0.872608682857143

00:08:19.120 --> 00:08:21.640 this would be an important process

NOTE Confidence: 0.872608682857143

00:08:21.640 --> 00:08:24.262 to study so that we could try and

NOTE Confidence: 0.872608682857143

00:08:24.262 --> 00:08:25.980 make these treatments more effective

NOTE Confidence: 0.872608682857143

00:08:25.980 --> 00:08:27.868 and potentially identify targets

NOTE Confidence: 0.872608682857143

00:08:27.868 --> 00:08:29.756 for new treatment development.

NOTE Confidence: 0.94891822

00:08:31.960 --> 00:08:32.880 So with that in mind,

NOTE Confidence: 0.94891822

00:08:32.880 --> 00:08:34.920 we started the Glioma Longitudinal

NOTE Confidence: 0.94891822

00:08:34.920 --> 00:08:38.600 Analysis or Glass Consortium in 2015.

NOTE Confidence: 0.94891822

00:08:38.600 --> 00:08:41.715 The glass consortium has set out to

NOTE Confidence: 0.94891822

00:08:41.720 --> 00:08:43.890 developed on the tail ends of the

NOTE Confidence: 0.94891822

00:08:43.890 --> 00:08:46.979 TCGA and it set out to develop a
NOTE Confidence: 0.94891822

00:08:46.979 --> 00:08:48.499 comprehensive molecular reference data
NOTE Confidence: 0.94891822

00:08:48.499 --> 00:08:51.502 set from pairs of tumors obtained and
NOTE Confidence: 0.94891822

00:08:51.502 --> 00:08:53.400 diagnosis and then after treatment,
NOTE Confidence: 0.94891822

00:08:53.400 --> 00:08:55.200 so the first tumor recurrence.
NOTE Confidence: 0.94891822

00:08:55.200 --> 00:08:57.265 But in reality we have been collecting
NOTE Confidence: 0.94891822

00:08:57.265 --> 00:08:59.119 tumors along the whole trajectory.
NOTE Confidence: 0.94891822

00:08:59.120 --> 00:09:01.955 So we have cases now for glass where we
NOTE Confidence: 0.94891822

00:09:01.955 --> 00:09:04.252 have 6 recurrences consecutively and
NOTE Confidence: 0.94891822

00:09:04.252 --> 00:09:06.196 we've molecularly characterized them.
NOTE Confidence: 0.94891822

00:09:06.200 --> 00:09:08.156 In other words, we've sequenced them.
NOTE Confidence: 0.94891822

00:09:08.160 --> 00:09:09.840 And then critically for glass,
NOTE Confidence: 0.94891822

00:09:09.840 --> 00:09:13.753 we really try to curate and obtain
NOTE Confidence: 0.94891822

00:09:13.753 --> 00:09:17.024 clinical annotation for all cases in
NOTE Confidence: 0.94891822

00:09:17.024 --> 00:09:20.084 the cohort because the value of a
NOTE Confidence: 0.94891822

00:09:20.084 --> 00:09:22.039 resource like this is significantly

NOTE Confidence: 0.94891822

00:09:22.039 --> 00:09:24.158 amplified if we know which tumors

NOTE Confidence: 0.94891822

00:09:24.158 --> 00:09:26.280 got treated in between time plans.

NOTE Confidence: 0.94891822

00:09:26.280 --> 00:09:28.401 Now why that we needed to do

NOTE Confidence: 0.94891822

00:09:28.401 --> 00:09:29.720 a consortium for this,

NOTE Confidence: 0.94891822

00:09:29.720 --> 00:09:31.568 it's because of things like patient

NOTE Confidence: 0.94891822

00:09:31.568 --> 00:09:33.799 mobility and the way tumor banks work.

NOTE Confidence: 0.94891822

00:09:33.800 --> 00:09:36.480 If you go to your average tumor bank,

NOTE Confidence: 0.94891822

00:09:36.480 --> 00:09:38.958 surely you'll find some tumors for which

NOTE Confidence: 0.94891822

00:09:38.958 --> 00:09:40.999 there's multiple time point specimens.

NOTE Confidence: 0.94891822

00:09:41.000 --> 00:09:43.016 But even for MD Anderson where I

NOTE Confidence: 0.94891822

00:09:43.016 --> 00:09:45.580 used to where we used to be one of

NOTE Confidence: 0.94891822

00:09:45.580 --> 00:09:48.040 the largest centers in the country,

NOTE Confidence: 0.94891822

00:09:48.040 --> 00:09:49.916 we were limited to a few dozen

NOTE Confidence: 0.94891822

00:09:49.916 --> 00:09:51.902 cases where we would have these

NOTE Confidence: 0.94891822

00:09:51.902 --> 00:09:53.398 multi time point specimens.

NOTE Confidence: 0.94891822

00:09:53.400 --> 00:09:55.080 And then as you're dealing with
NOTE Confidence: 0.94891822

00:09:55.080 --> 00:09:56.410 attrition due to tissue quality,
NOTE Confidence: 0.94891822

00:09:56.410 --> 00:09:57.880 at the end of the day,
NOTE Confidence: 0.94891822

00:09:57.880 --> 00:10:00.180 you really need an international
NOTE Confidence: 0.94891822

00:10:00.180 --> 00:10:03.437 collaboration to get to the large enough
NOTE Confidence: 0.94891822

00:10:03.437 --> 00:10:06.756 numbers to do any kind of robust analysis.
NOTE Confidence: 0.94891822

00:10:06.760 --> 00:10:08.956 So we started the consortium also
NOTE Confidence: 0.94891822

00:10:08.956 --> 00:10:11.110 still being enthusiastic of how well
NOTE Confidence: 0.94891822

00:10:11.110 --> 00:10:13.000 the TCJ collaboration went for us
NOTE Confidence: 0.94891822

00:10:13.000 --> 00:10:15.346 and now have developed a consortium
NOTE Confidence: 0.94891822

00:10:15.346 --> 00:10:17.334 that involves over 140 people
NOTE Confidence: 0.94891822

00:10:17.334 --> 00:10:19.369 spread across the globe essentially
NOTE Confidence: 0.94891822

00:10:19.369 --> 00:10:21.320 in 14 different countries.
NOTE Confidence: 0.94891822

00:10:21.320 --> 00:10:22.958 This is an older picture actually.
NOTE Confidence: 0.94891822

00:10:22.960 --> 00:10:24.038 If you would take a picture now,
NOTE Confidence: 0.94891822

00:10:24.040 --> 00:10:24.800 it would fill the room.

NOTE Confidence: 0.92655475

00:10:27.320 --> 00:10:30.608 So an important purpose of Glass

NOTE Confidence: 0.92655475

00:10:30.608 --> 00:10:33.440 is not just to create this,

NOTE Confidence: 0.92655475

00:10:33.440 --> 00:10:36.272 this data set but also to share it

NOTE Confidence: 0.92655475

00:10:36.272 --> 00:10:38.468 broadly just like the TCA so that

NOTE Confidence: 0.92655475

00:10:38.468 --> 00:10:39.992 not just we can do interesting

NOTE Confidence: 0.92655475

00:10:39.992 --> 00:10:41.532 analysis with them but of course

NOTE Confidence: 0.92655475

00:10:41.532 --> 00:10:43.200 that the whole community can do so.

NOTE Confidence: 0.92655475

00:10:43.200 --> 00:10:45.727 So in 2022 we released our latest

NOTE Confidence: 0.92655475

00:10:45.727 --> 00:10:47.921 public version of the glass data

NOTE Confidence: 0.92655475

00:10:47.921 --> 00:10:50.401 resource which is a cohort of 300

NOTE Confidence: 0.92655475

00:10:50.401 --> 00:10:53.208 / 300 patients for whom we have

NOTE Confidence: 0.92655475

00:10:53.208 --> 00:10:55.155 collected multi timepoint DNA

NOTE Confidence: 0.92655475

00:10:55.155 --> 00:10:57.800 sequencing and or RNA sequencing.

NOTE Confidence: 0.92655475

00:10:57.800 --> 00:10:59.584 Now these 300 patients and I can tell

NOTE Confidence: 0.92655475

00:10:59.584 --> 00:11:01.573 you in the meantime now we're 2024,

NOTE Confidence: 0.92655475

00:11:01.573 --> 00:11:03.811 we've nearly doubled the cohort size

NOTE Confidence: 0.92655475

00:11:03.811 --> 00:11:06.358 and we'll be releasing that soon.

NOTE Confidence: 0.92655475

00:11:06.360 --> 00:11:08.220 So we continue to actively expand

NOTE Confidence: 0.92655475

00:11:08.220 --> 00:11:08.840 this cohort

NOTE Confidence: 0.863402449230769

00:11:10.880 --> 00:11:12.238 Right now in our code if you

NOTE Confidence: 0.863402449230769

00:11:12.238 --> 00:11:13.638 go to the URL shown here,

NOTE Confidence: 0.863402449230769

00:11:13.640 --> 00:11:16.376 you can find variants in clinical

NOTE Confidence: 0.863402449230769

00:11:16.376 --> 00:11:19.112 annotation for over 300 cases of

NOTE Confidence: 0.863402449230769

00:11:19.112 --> 00:11:22.136 which in majority are from IDH wild

NOTE Confidence: 0.863402449230769

00:11:22.136 --> 00:11:24.280 type tumors followed by the non

NOTE Confidence: 0.863402449230769

00:11:24.280 --> 00:11:26.140 Codells Finally the Codells as you

NOTE Confidence: 0.863402449230769

00:11:26.140 --> 00:11:28.170 can see we have a relative under

NOTE Confidence: 0.863402449230769

00:11:28.170 --> 00:11:29.604 representation of Codells here and

NOTE Confidence: 0.863402449230769

00:11:29.604 --> 00:11:31.308 that's likely due to the longer

NOTE Confidence: 0.863402449230769

00:11:31.308 --> 00:11:33.225 time to recurrence or Codell tumors

NOTE Confidence: 0.863402449230769

00:11:33.225 --> 00:11:35.355 compared to IDs wild type tumors.

NOTE Confidence: 0.863402449230769

00:11:35.360 --> 00:11:37.598 The shorter the time to recurrence,

NOTE Confidence: 0.863402449230769

00:11:37.600 --> 00:11:39.518 the higher the likelihood that two tumor

NOTE Confidence: 0.863402449230769

00:11:39.518 --> 00:11:41.597 specimens will end up in the same tumor bank.

NOTE Confidence: 0.863402449230769

00:11:41.600 --> 00:11:44.360 In addition to that RE resection is not

NOTE Confidence: 0.863402449230769

00:11:44.360 --> 00:11:47.192 standard for any of these and so that's

NOTE Confidence: 0.863402449230769

00:11:47.192 --> 00:11:49.639 another factor that comes into play here.

NOTE Confidence: 0.863402449230769

00:11:49.640 --> 00:11:51.650 You can maybe appreciate that the

NOTE Confidence: 0.863402449230769

00:11:51.650 --> 00:11:54.204 median age of diagnosis in these

NOTE Confidence: 0.863402449230769

00:11:54.204 --> 00:11:56.559 three groups is relatively young.

NOTE Confidence: 0.863402449230769

00:11:56.560 --> 00:11:59.480 And that is because in order to end up for

NOTE Confidence: 0.863402449230769

00:11:59.480 --> 00:12:01.640 data to end up in our in our resource,

NOTE Confidence: 0.863402449230769

00:12:01.640 --> 00:12:05.656 the patient has to have had two surgical

NOTE Confidence: 0.863402449230769

00:12:05.656 --> 00:12:07.880 procedures in order to obtain specimens,

NOTE Confidence: 0.863402449230769

00:12:07.880 --> 00:12:09.644 meaning that the patient has had to

NOTE Confidence: 0.863402449230769

00:12:09.644 --> 00:12:11.529 be in relatively good shape to be

NOTE Confidence: 0.863402449230769

00:12:11.529 --> 00:12:12.874 able to undergo those procedures.
NOTE Confidence: 0.863402449230769

00:12:12.880 --> 00:12:15.157 So we see a bit of a bias in
NOTE Confidence: 0.863402449230769

00:12:15.157 --> 00:12:17.836 median aid to diagnosis as well as
NOTE Confidence: 0.863402449230769

00:12:17.836 --> 00:12:19.840 in survival patterns shown here.
NOTE Confidence: 0.863402449230769

00:12:19.840 --> 00:12:20.520 That is what it is.
NOTE Confidence: 0.863402449230769

00:12:20.520 --> 00:12:22.960 We can't really address that.
NOTE Confidence: 0.863402449230769

00:12:22.960 --> 00:12:25.004 We try to address it by expanding
NOTE Confidence: 0.863402449230769

00:12:25.004 --> 00:12:26.845 the resources large as we can so
NOTE Confidence: 0.863402449230769

00:12:26.845 --> 00:12:28.536 that we kept capture as many patient
NOTE Confidence: 0.863402449230769

00:12:28.536 --> 00:12:29.640 groups as we can.
NOTE Confidence: 0.863402449230769

00:12:29.640 --> 00:12:31.537 Finally, I'm going to point out that
NOTE Confidence: 0.863402449230769

00:12:31.537 --> 00:12:33.758 our annotation in my opinion is really great.
NOTE Confidence: 0.863402449230769

00:12:33.760 --> 00:12:35.986 So we know for all patients whether
NOTE Confidence: 0.863402449230769

00:12:35.986 --> 00:12:37.839 they or nearly all patients,
NOTE Confidence: 0.863402449230769

00:12:37.840 --> 00:12:39.560 whether they have received tamizolamides,
NOTE Confidence: 0.863402449230769

00:12:39.560 --> 00:12:41.268 yes or no and whether they have

NOTE Confidence: 0.863402449230769
00:12:41.268 --> 00:12:42.400 received radio radiation therapy,
NOTE Confidence: 0.863402449230769
00:12:42.400 --> 00:12:43.396 yes or no.
NOTE Confidence: 0.863402449230769
00:12:43.396 --> 00:12:45.720 And we've got many more clinical variables.
NOTE Confidence: 0.863402449230769
00:12:45.720 --> 00:12:47.400 I just chose to highlight these
NOTE Confidence: 0.863402449230769
00:12:47.400 --> 00:12:49.599 on this on this particular slide.
NOTE Confidence: 0.863402449230769
00:12:49.600 --> 00:12:50.520 So I, in my opinion,
NOTE Confidence: 0.863402449230769
00:12:50.520 --> 00:12:54.600 it's really becoming a phenomenal resource.
NOTE Confidence: 0.863402449230769
00:12:54.600 --> 00:12:56.280 Now what can you do with a
NOTE Confidence: 0.863402449230769
00:12:56.280 --> 00:12:57.000 resource like this?
NOTE Confidence: 0.863402449230769
00:12:57.000 --> 00:12:58.197 I think you can do many things.
NOTE Confidence: 0.863402449230769
00:12:58.200 --> 00:12:59.636 But we initially started,
NOTE Confidence: 0.863402449230769
00:12:59.636 --> 00:13:01.072 we initially focused on
NOTE Confidence: 0.863402449230769
00:13:01.072 --> 00:13:02.440 2 important questions.
NOTE Confidence: 0.863402449230769
00:13:02.440 --> 00:13:02.814 First,
NOTE Confidence: 0.863402449230769
00:13:02.814 --> 00:13:05.432 what is the impact of temozolomide on
NOTE Confidence: 0.863402449230769

00:13:05.432 --> 00:13:07.557 tumor evolution and on these gliomas?
NOTE Confidence: 0.863402449230769

00:13:07.560 --> 00:13:08.090 And 2nd,
NOTE Confidence: 0.863402449230769

00:13:08.090 --> 00:13:09.680 what is the impact of radiation?
NOTE Confidence: 0.633319481

00:13:13.200 --> 00:13:14.960 So treatment with temozolomite.
NOTE Confidence: 0.633319481

00:13:14.960 --> 00:13:17.600 Temozolomite is a DE alkylating agent.
NOTE Confidence: 0.633319481

00:13:17.600 --> 00:13:20.408 The repair process of the DE
NOTE Confidence: 0.633319481

00:13:20.408 --> 00:13:23.490 alkylation shows up in can show up
NOTE Confidence: 0.633319481

00:13:23.490 --> 00:13:26.000 as mutations and nucleotide changes.
NOTE Confidence: 0.633319481

00:13:26.000 --> 00:13:28.140 Nucleotide changes can conveniently
NOTE Confidence: 0.633319481

00:13:28.140 --> 00:13:30.280 be detected using sequencing,
NOTE Confidence: 0.633319481

00:13:30.280 --> 00:13:32.431 and that means that in a subset of tumors
NOTE Confidence: 0.633319481

00:13:32.431 --> 00:13:34.278 that are treated with temozolomide,
NOTE Confidence: 0.633319481

00:13:34.280 --> 00:13:36.920 A hypermutation phenotype will develop.
NOTE Confidence: 0.633319481

00:13:36.920 --> 00:13:38.378 So these are tumors where cells
NOTE Confidence: 0.633319481

00:13:38.378 --> 00:13:40.148 have been able to overcome the
NOTE Confidence: 0.633319481

00:13:40.148 --> 00:13:41.636 damaging effect of temozolomide,

NOTE Confidence: 0.633319481

00:13:41.640 --> 00:13:43.628 and they do so by repairing the

NOTE Confidence: 0.633319481

00:13:43.628 --> 00:13:45.320 damage caused by temozolomide,

NOTE Confidence: 0.633319481

00:13:45.320 --> 00:13:47.240 and the damage is then showing

NOTE Confidence: 0.633319481

00:13:47.240 --> 00:13:48.200 up as hypermutation.

NOTE Confidence: 0.633319481

00:13:48.200 --> 00:13:49.800 Very high mutational burdens

NOTE Confidence: 0.901563641666667

00:13:51.880 --> 00:13:54.211 across our cohort and this is slightly

NOTE Confidence: 0.901563641666667

00:13:54.211 --> 00:13:56.057 older version of our data set.

NOTE Confidence: 0.901563641666667

00:13:56.057 --> 00:13:58.136 But across our cohort we then see

NOTE Confidence: 0.901563641666667

00:13:58.136 --> 00:13:59.857 that when we compare mutational

NOTE Confidence: 0.901563641666667

00:13:59.857 --> 00:14:02.328 burden of the initial tumor and the

NOTE Confidence: 0.901563641666667

00:14:02.394 --> 00:14:04.439 post TMZ treated recurrent tumor,

NOTE Confidence: 0.901563641666667

00:14:04.440 --> 00:14:07.716 so this is only TMZ treated cases,

NOTE Confidence: 0.901563641666667

00:14:07.720 --> 00:14:09.666 we see very high mutational burdens in

NOTE Confidence: 0.901563641666667

00:14:09.666 --> 00:14:11.477 these recurrences and this is a log scale.

NOTE Confidence: 0.901563641666667

00:14:11.480 --> 00:14:13.545 So we chose a cutoff of 10

NOTE Confidence: 0.901563641666667

00:14:13.545 --> 00:14:14.800 mutations per megabase here.
NOTE Confidence: 0.879999231428572

00:14:16.840 --> 00:14:20.116 So across the three subtypes of glioma,
NOTE Confidence: 0.879999231428572

00:14:20.120 --> 00:14:23.920 we see that a subset recurs as hypermutated.
NOTE Confidence: 0.879999231428572

00:14:23.920 --> 00:14:27.040 The relative frequencies differ by subtypes,
NOTE Confidence: 0.879999231428572

00:14:27.040 --> 00:14:29.820 ID 12 type tumors 15 to 16%.
NOTE Confidence: 0.879999231428572

00:14:29.820 --> 00:14:32.120 For the IDH mutant tumors,
NOTE Confidence: 0.879999231428572

00:14:32.120 --> 00:14:35.011 we see that the rate of hypermutation
NOTE Confidence: 0.879999231428572

00:14:35.011 --> 00:14:36.840 development is much higher.
NOTE Confidence: 0.879999231428572

00:14:36.840 --> 00:14:38.955 We think this is due to the fact that
NOTE Confidence: 0.879999231428572

00:14:38.960 --> 00:14:42.117 IDH mutated tumors take longer to recur.
NOTE Confidence: 0.879999231428572

00:14:42.120 --> 00:14:44.094 Therefore, there's a more of an
NOTE Confidence: 0.879999231428572

00:14:44.094 --> 00:14:45.880 opportunity for hypermutation to develop.
NOTE Confidence: 0.8969933675

00:14:50.160 --> 00:14:52.300 Hypermutation has been associated
NOTE Confidence: 0.8969933675

00:14:52.300 --> 00:14:54.440 with relatively poor outcomes.
NOTE Confidence: 0.8969933675

00:14:54.440 --> 00:14:56.582 What we found when we EPL evaluated
NOTE Confidence: 0.8969933675

00:14:56.582 --> 00:14:57.935 the presence of hypermutation

NOTE Confidence: 0.8969933675

00:14:57.935 --> 00:15:00.137 in TMZ treated tumors and then

NOTE Confidence: 0.8969933675

00:15:00.137 --> 00:15:02.200 compared to time to progression,

NOTE Confidence: 0.8969933675

00:15:02.200 --> 00:15:03.776 that it's actually similar

NOTE Confidence: 0.8969933675

00:15:03.776 --> 00:15:04.958 between non hypermutated.

NOTE Confidence: 0.8969933675

00:15:04.960 --> 00:15:07.627 So tumors that did not become hypermutated

NOTE Confidence: 0.8969933675

00:15:07.627 --> 00:15:10.359 versus those that did become hypermutated.

NOTE Confidence: 0.8969933675

00:15:10.360 --> 00:15:12.730 So time to progression doesn't really

NOTE Confidence: 0.8969933675

00:15:12.730 --> 00:15:15.440 depend on the development of hypermutation,

NOTE Confidence: 0.8969933675

00:15:15.440 --> 00:15:17.918 but once a tumor has become hypermutated,

NOTE Confidence: 0.8969933675

00:15:17.920 --> 00:15:19.870 so after that recurrence the hypermutators

NOTE Confidence: 0.8969933675

00:15:19.870 --> 00:15:22.199 do worse than the non hypermutators.

NOTE Confidence: 0.862874347307692

00:15:26.040 --> 00:15:28.736 That's not to say that we shouldn't be

NOTE Confidence: 0.862874347307692

00:15:28.736 --> 00:15:31.199 treating these patients with tenozolamide.

NOTE Confidence: 0.862874347307692

00:15:31.200 --> 00:15:33.784 Clinical trials such as the CAD non study

NOTE Confidence: 0.862874347307692

00:15:33.784 --> 00:15:36.104 from the ERTC have clearly demonstrated

NOTE Confidence: 0.862874347307692

00:15:36.104 --> 00:15:38.120 that temozolomide has significant
NOTE Confidence: 0.862874347307692

00:15:38.120 --> 00:15:40.640 benefits across the patient population.
NOTE Confidence: 0.862874347307692

00:15:40.640 --> 00:15:42.600 So even though sometimes people will argue,
NOTE Confidence: 0.862874347307692

00:15:42.600 --> 00:15:45.388 well temozolomide causes hypermutation,
NOTE Confidence: 0.862874347307692

00:15:45.388 --> 00:15:47.479 hypermutation is bad.
NOTE Confidence: 0.862874347307692

00:15:47.480 --> 00:15:49.360 As a patient group,
NOTE Confidence: 0.862874347307692

00:15:49.360 --> 00:15:51.240 temozolomide is clearly beneficial.
NOTE Confidence: 0.755153718571429

00:15:55.680 --> 00:16:00.185 Emma and Kevin in our lab then chose
NOTE Confidence: 0.755153718571429

00:16:00.185 --> 00:16:02.255 to study similar questions but then
NOTE Confidence: 0.755153718571429

00:16:02.255 --> 00:16:04.487 for response to radiation therapy which
NOTE Confidence: 0.755153718571429

00:16:04.487 --> 00:16:07.119 causes a different type of DNA damage.
NOTE Confidence: 0.755153718571429

00:16:07.120 --> 00:16:08.794 It causes single single strand breaks
NOTE Confidence: 0.755153718571429

00:16:08.794 --> 00:16:10.680 as well as double strand breaks.
NOTE Confidence: 0.927245286666667

00:16:14.280 --> 00:16:16.572 And Long story short,
NOTE Confidence: 0.927245286666667

00:16:16.572 --> 00:16:19.437 they discovered that when comparing
NOTE Confidence: 0.927245286666667

00:16:19.440 --> 00:16:21.714 cases not treated with radiation to

NOTE Confidence: 0.927245286666667

00:16:21.714 --> 00:16:24.279 those that are treated with radiation,

NOTE Confidence: 0.927245286666667

00:16:24.280 --> 00:16:27.450 that treated cases develop a

NOTE Confidence: 0.927245286666667

00:16:27.450 --> 00:16:30.080 relatively high number of small 2

NOTE Confidence: 0.927245286666667

00:16:30.080 --> 00:16:32.120 to 20 base pair deletions across

NOTE Confidence: 0.927245286666667

00:16:32.190 --> 00:16:34.640 their scattered across their genome.

NOTE Confidence: 0.927245286666667

00:16:34.640 --> 00:16:36.684 So it's a bit of a similar

NOTE Confidence: 0.927245286666667

00:16:36.684 --> 00:16:37.560 phenomenon to hypermutation,

NOTE Confidence: 0.927245286666667

00:16:37.560 --> 00:16:40.680 but instead of single nucleotide changes,

NOTE Confidence: 0.927245286666667

00:16:40.680 --> 00:16:43.830 we found that radiation drives small

NOTE Confidence: 0.927245286666667

00:16:43.830 --> 00:16:46.148 deletions and in the treated cases we

NOTE Confidence: 0.927245286666667

00:16:46.148 --> 00:16:47.765 see significantly more small deletions

NOTE Confidence: 0.927245286666667

00:16:47.765 --> 00:16:49.955 arise compared to the untreated cases.

NOTE Confidence: 0.803673755555556

00:16:52.640 --> 00:16:54.805 Now radiation and temozolomide are

NOTE Confidence: 0.803673755555556

00:16:54.805 --> 00:16:57.393 often used in combination its standard

NOTE Confidence: 0.803673755555556

00:16:57.393 --> 00:16:59.878 of care for IDH wild type tumors.

NOTE Confidence: 0.803673755555556

00:16:59.880 --> 00:17:02.484 So are we observing this increase in
NOTE Confidence: 0.803673755555556

00:17:02.484 --> 00:17:04.944 small deletions because some of these
NOTE Confidence: 0.803673755555556

00:17:04.944 --> 00:17:07.074 tumors will are developing hypermutation?
NOTE Confidence: 0.904342775

00:17:11.360 --> 00:17:13.478 The answer is yes and no.
NOTE Confidence: 0.904342775

00:17:13.480 --> 00:17:15.808 Meaning that when we split up our cohort
NOTE Confidence: 0.904342775

00:17:15.808 --> 00:17:17.956 in those cases that are hypermutated
NOTE Confidence: 0.904342775

00:17:17.956 --> 00:17:19.836 as well as radiation treated,
NOTE Confidence: 0.904342775

00:17:19.840 --> 00:17:21.896 we find that hypermutation
NOTE Confidence: 0.904342775

00:17:21.896 --> 00:17:23.734 independent of radiation actually.
NOTE Confidence: 0.904342775

00:17:23.734 --> 00:17:25.792 So these are tumors that are hypermutated
NOTE Confidence: 0.904342775

00:17:25.792 --> 00:17:27.957 and have not been treated with radiation
NOTE Confidence: 0.904342775

00:17:27.960 --> 00:17:31.918 that they also show an increase
NOTE Confidence: 0.904342775

00:17:31.918 --> 00:17:34.234 in the number of small deletions.
NOTE Confidence: 0.904342775

00:17:34.240 --> 00:17:34.900 But importantly,
NOTE Confidence: 0.904342775

00:17:34.900 --> 00:17:37.210 those that are not have been mutated
NOTE Confidence: 0.904342775

00:17:37.210 --> 00:17:39.465 and have been radiated also show

NOTE Confidence: 0.904342775

00:17:39.465 --> 00:17:40.957 that small deletion increase.

NOTE Confidence: 0.904342775

00:17:40.960 --> 00:17:43.156 So hypermutation and radiation

NOTE Confidence: 0.904342775

00:17:43.156 --> 00:17:45.352 are independent factors driving

NOTE Confidence: 0.904342775

00:17:45.352 --> 00:17:47.920 the increase in small deletions.

NOTE Confidence: 0.904342775

00:17:47.920 --> 00:17:49.636 And in that sense small deletions,

NOTE Confidence: 0.904342775

00:17:49.640 --> 00:17:51.784 the small deletion increase

NOTE Confidence: 0.904342775

00:17:51.784 --> 00:17:54.464 burden increase is comparable to

NOTE Confidence: 0.904342775

00:17:54.464 --> 00:17:56.440 hypermutation for actemazolamide.

NOTE Confidence: 0.904342775

00:17:56.440 --> 00:17:58.528 And in our paper we actually found

NOTE Confidence: 0.904342775

00:17:58.528 --> 00:18:00.199 that this is true across cancers,

NOTE Confidence: 0.904342775

00:18:00.200 --> 00:18:00.998 not just gliomas,

NOTE Confidence: 0.63602453

00:18:03.960 --> 00:18:06.150 Gemma and Kevin and also evaluated

NOTE Confidence: 0.63602453

00:18:06.150 --> 00:18:07.684 aneuploidies, in other words,

NOTE Confidence: 0.63602453

00:18:07.684 --> 00:18:09.236 broad losses and gains.

NOTE Confidence: 0.63602453

00:18:09.240 --> 00:18:11.295 So while small deletions will

NOTE Confidence: 0.63602453

00:18:11.295 --> 00:18:13.350 arise from double strand breaks
NOTE Confidence: 0.63602453

00:18:13.427 --> 00:18:15.519 that are subsequently repaired,
NOTE Confidence: 0.63602453

00:18:15.520 --> 00:18:17.024 anuploidies typically are a
NOTE Confidence: 0.63602453

00:18:17.024 --> 00:18:19.280 result of cell cycle of errors.
NOTE Confidence: 0.63602453

00:18:19.280 --> 00:18:21.100 During the cell cycle,
NOTE Confidence: 0.63602453

00:18:21.100 --> 00:18:22.920 for example MIS segregation,
NOTE Confidence: 0.748935986666667

00:18:25.240 --> 00:18:28.012 we compared gains, broad gains and
NOTE Confidence: 0.748935986666667

00:18:28.012 --> 00:18:31.416 broad losses and we did that between
NOTE Confidence: 0.748935986666667

00:18:31.416 --> 00:18:33.432 irradiated cases and unirradiated
NOTE Confidence: 0.748935986666667

00:18:33.432 --> 00:18:36.840 cases and found no difference in gains.
NOTE Confidence: 0.748935986666667

00:18:36.840 --> 00:18:39.000 But we found a significantly higher
NOTE Confidence: 0.748935986666667

00:18:39.000 --> 00:18:42.580 number of whole chromosome arm losses in
NOTE Confidence: 0.748935986666667

00:18:42.580 --> 00:18:45.440 irradiated versus non irradiated tumors.
NOTE Confidence: 0.748935986666667

00:18:45.440 --> 00:18:47.240 Similar to the small deletion increase,
NOTE Confidence: 0.797274444

00:18:49.680 --> 00:18:51.440 now homocygous deletion of CDK
NOTE Confidence: 0.797274444

00:18:51.440 --> 00:18:54.684 into A which is of course a cell

NOTE Confidence: 0.797274444

00:18:54.684 --> 00:18:57.024 cycle regulator has previously been

NOTE Confidence: 0.797274444

00:18:57.024 --> 00:18:59.296 associated with tumor progression

NOTE Confidence: 0.797274444

00:18:59.296 --> 00:19:02.636 especially in Ida mutant tumors.

NOTE Confidence: 0.797274444

00:19:02.640 --> 00:19:05.020 We compared not just homozygous

NOTE Confidence: 0.797274444

00:19:05.020 --> 00:19:07.400 deletion but also hemisygous deletion

NOTE Confidence: 0.797274444

00:19:07.474 --> 00:19:10.178 of CDK and to a first in untreated

NOTE Confidence: 0.797274444

00:19:10.178 --> 00:19:12.064 initial tumors in glass this is

NOTE Confidence: 0.797274444

00:19:12.064 --> 00:19:14.108 codels and non codels and this is

NOTE Confidence: 0.797274444

00:19:14.108 --> 00:19:15.919 focusing on the IDH mutant tumors,

NOTE Confidence: 0.797274444

00:19:15.920 --> 00:19:18.075 Codels versus non codels first

NOTE Confidence: 0.797274444

00:19:18.075 --> 00:19:20.682 and we find that non codels have

NOTE Confidence: 0.797274444

00:19:20.682 --> 00:19:23.208 a higher rate of CDK and to a

NOTE Confidence: 0.797274444

00:19:23.208 --> 00:19:25.554 homozygous as well as semisygous loss,

NOTE Confidence: 0.797274444

00:19:25.560 --> 00:19:28.110 but this is particular particularly

NOTE Confidence: 0.797274444

00:19:28.110 --> 00:19:29.640 pronounced in recurrences.

NOTE Confidence: 0.797274444

00:19:29.640 --> 00:19:32.100 So at recurrence non codal IDH
NOTE Confidence: 0.797274444

00:19:32.100 --> 00:19:34.136 mutant tumors significantly show
NOTE Confidence: 0.797274444

00:19:34.136 --> 00:19:36.504 a significant increase in the
NOTE Confidence: 0.797274444

00:19:36.504 --> 00:19:38.408 number of CDK N to a homozygous
NOTE Confidence: 0.797274444

00:19:38.408 --> 00:19:40.680 as well as hemisygous deletions.
NOTE Confidence: 0.797274444

00:19:40.680 --> 00:19:43.800 And this is then particularly true
NOTE Confidence: 0.797274444

00:19:43.800 --> 00:19:45.845 amongst irradiated tumors suggesting
NOTE Confidence: 0.797274444

00:19:45.845 --> 00:19:48.270 that there's a relationship between
NOTE Confidence: 0.797274444

00:19:48.270 --> 00:19:50.200 irradiation and CDK N to a loss.
NOTE Confidence: 0.637069474615385

00:19:53.280 --> 00:19:55.835 And again the presence or the when
NOTE Confidence: 0.637069474615385

00:19:55.835 --> 00:19:58.884 a CDK N to a loss either hemisygous
NOTE Confidence: 0.637069474615385

00:19:58.884 --> 00:20:01.594 or homozygous has been acquired,
NOTE Confidence: 0.637069474615385

00:20:01.600 --> 00:20:03.856 we see that that correlates associates
NOTE Confidence: 0.637069474615385

00:20:03.856 --> 00:20:06.040 with worse outcomes to treatment.
NOTE Confidence: 0.827214079

00:20:09.960 --> 00:20:12.528 We then evaluated the association between
NOTE Confidence: 0.827214079

00:20:12.528 --> 00:20:16.640 these broad aneuploidies and CDK into a loss.

NOTE Confidence: 0.827214079

00:20:16.640 --> 00:20:19.314 Here we grouped a bunch of cases.

NOTE Confidence: 0.827214079

00:20:19.320 --> 00:20:20.556 Actually this is not class data,

NOTE Confidence: 0.827214079

00:20:20.560 --> 00:20:22.240 this is span cancer data.

NOTE Confidence: 0.827214079

00:20:22.240 --> 00:20:25.548 We grouped those cases by non irradiated.

NOTE Confidence: 0.827214079

00:20:25.548 --> 00:20:26.656 Palliatively irradiated.

NOTE Confidence: 0.827214079

00:20:26.656 --> 00:20:30.030 So lower doses and accuratively irradiated

NOTE Confidence: 0.827214079

00:20:30.030 --> 00:20:33.632 tumors and find that the increase in

NOTE Confidence: 0.827214079

00:20:33.632 --> 00:20:35.888 the number of chromosome losses is

NOTE Confidence: 0.827214079

00:20:35.888 --> 00:20:38.143 actually only found in tumors that

NOTE Confidence: 0.827214079

00:20:38.143 --> 00:20:40.480 have homozygous deletion of CDK into A.

NOTE Confidence: 0.827214079

00:20:40.480 --> 00:20:43.010 So while we previously showed

NOTE Confidence: 0.827214079

00:20:43.010 --> 00:20:45.034 that irradiation appears to

NOTE Confidence: 0.827214079

00:20:45.034 --> 00:20:47.558 drive broad chromosome losses,

NOTE Confidence: 0.827214079

00:20:47.560 --> 00:20:50.518 what we're actually seeing is that

NOTE Confidence: 0.827214079

00:20:50.518 --> 00:20:53.316 irradiation associates with CDK into a loss,

NOTE Confidence: 0.827214079

00:20:53.316 --> 00:20:56.270 and it's really the CDK into a loss
NOTE Confidence: 0.827214079

00:20:56.270 --> 00:20:58.520 that then associates with aneuploidy
NOTE Confidence: 0.827214079

00:20:58.520 --> 00:21:00.040 because we're seeing a significant
NOTE Confidence: 0.827214079

00:21:00.040 --> 00:21:02.048 increase in the number of chromosome
NOTE Confidence: 0.827214079

00:21:02.048 --> 00:21:04.376 losses in unirradiated cases when
NOTE Confidence: 0.827214079

00:21:04.376 --> 00:21:08.240 homozygous loss of CDK into A is present.
NOTE Confidence: 0.827214079

00:21:08.240 --> 00:21:10.015 So irradiation itself does not
NOTE Confidence: 0.827214079

00:21:10.015 --> 00:21:11.435 appear to drive aneuploidy.
NOTE Confidence: 0.827214079

00:21:11.440 --> 00:21:13.160 It appears to drive CDK into a loss,
NOTE Confidence: 0.827214079

00:21:13.160 --> 00:21:14.440 which then drives to aneuploidy.
NOTE Confidence: 0.832404651666667

00:21:17.400 --> 00:21:20.640 And as with the hypermutation example,
NOTE Confidence: 0.832404651666667

00:21:20.640 --> 00:21:22.360 we're finding no significant
NOTE Confidence: 0.832404651666667

00:21:22.360 --> 00:21:24.744 difference in surgical interval in
NOTE Confidence: 0.832404651666667

00:21:24.744 --> 00:21:27.880 irradiated cases associating with the
NOTE Confidence: 0.832404651666667

00:21:27.880 --> 00:21:30.280 number of acquired small deletions.
NOTE Confidence: 0.832404651666667

00:21:30.280 --> 00:21:31.240 But post recurrence,

NOTE Confidence: 0.832404651666667

00:21:31.240 --> 00:21:33.160 those tumors that acquire the most,

NOTE Confidence: 0.832404651666667

00:21:33.160 --> 00:21:35.350 the highest number of new small

NOTE Confidence: 0.832404651666667

00:21:35.350 --> 00:21:37.385 deletions are the ones that stop

NOTE Confidence: 0.832404651666667

00:21:37.385 --> 00:21:38.717 responding to further therapy

NOTE Confidence: 0.832404651666667

00:21:38.717 --> 00:21:40.519 that have very poor outcomes.

NOTE Confidence: 0.832404651666667

00:21:40.520 --> 00:21:42.935 So acquired small deletions are a marker

NOTE Confidence: 0.832404651666667

00:21:42.935 --> 00:21:45.279 for further tumor response if you will.

NOTE Confidence: 0.936510996666667

00:21:51.930 --> 00:21:53.046 So this is the model that

NOTE Confidence: 0.936510996666667

00:21:53.046 --> 00:21:54.209 seems to arise from our data,

NOTE Confidence: 0.936510996666667

00:21:54.210 --> 00:21:56.676 which is perhaps not super surprising.

NOTE Confidence: 0.936510996666667

00:21:56.680 --> 00:21:59.560 These tumors as I started with

NOTE Confidence: 0.936510996666667

00:21:59.560 --> 00:22:02.038 originate from a cell of origin

NOTE Confidence: 0.936510996666667

00:22:02.040 --> 00:22:03.440 that starts to expand more

NOTE Confidence: 0.936510996666667

00:22:03.440 --> 00:22:05.040 quickly than the cells around it.

NOTE Confidence: 0.936510996666667

00:22:05.040 --> 00:22:06.936 And upon bottlenecks in

NOTE Confidence: 0.936510996666667

00:22:06.936 --> 00:22:08.358 the tumor microenvironment,
NOTE Confidence: 0.936510996666667

00:22:08.360 --> 00:22:09.820 subclones will further arise that
NOTE Confidence: 0.936510996666667

00:22:09.820 --> 00:22:12.110 then at the time of the diagnosis
NOTE Confidence: 0.936510996666667

00:22:12.110 --> 00:22:14.040 can be detected through sequencing.
NOTE Confidence: 0.936510996666667

00:22:14.040 --> 00:22:16.115 Then we impose this therapeutic
NOTE Confidence: 0.936510996666667

00:22:16.115 --> 00:22:18.851 barrier for surgery and then a chemo
NOTE Confidence: 0.936510996666667

00:22:18.851 --> 00:22:20.485 and radio and those cancer cells that
NOTE Confidence: 0.936510996666667

00:22:20.485 --> 00:22:22.039 are able to repair the DNA damage.
NOTE Confidence: 0.936510996666667

00:22:22.040 --> 00:22:24.630 So the ones that have the hypermutation
NOTE Confidence: 0.936510996666667

00:22:24.630 --> 00:22:26.824 phenotype or the ones that have acquired
NOTE Confidence: 0.936510996666667

00:22:26.824 --> 00:22:28.680 large numbers of small deletions,
NOTE Confidence: 0.936510996666667

00:22:28.680 --> 00:22:30.264 those are the ones that are
NOTE Confidence: 0.936510996666667

00:22:30.264 --> 00:22:32.304 able to repair the A damage and
NOTE Confidence: 0.936510996666667

00:22:32.304 --> 00:22:34.160 can subsequently be detected,
NOTE Confidence: 0.936510996666667

00:22:34.160 --> 00:22:35.309 have expanded sufficiently,
NOTE Confidence: 0.936510996666667

00:22:35.309 --> 00:22:37.607 have become large enough subclones that

NOTE Confidence: 0.936510996666667
00:22:37.607 --> 00:22:39.960 we can detect them through sequencing.
NOTE Confidence: 0.936510996666667
00:22:39.960 --> 00:22:41.970 So then it's not surprising that
NOTE Confidence: 0.936510996666667
00:22:41.970 --> 00:22:43.651 in recurrence these tumors that
NOTE Confidence: 0.936510996666667
00:22:43.651 --> 00:22:44.999 have these genomic scars,
NOTE Confidence: 0.936510996666667
00:22:45.000 --> 00:22:46.495 these signatures are the ones
NOTE Confidence: 0.936510996666667
00:22:46.495 --> 00:22:48.394 that have poor outcomes and stop
NOTE Confidence: 0.936510996666667
00:22:48.394 --> 00:22:49.762 responding to treatment because
NOTE Confidence: 0.936510996666667
00:22:49.762 --> 00:22:51.814 you're looking at cells that have
NOTE Confidence: 0.936510996666667
00:22:51.814 --> 00:22:53.548 already been able to have already
NOTE Confidence: 0.936510996666667
00:22:53.548 --> 00:22:55.075 shown that they don't care about
NOTE Confidence: 0.936510996666667
00:22:55.075 --> 00:22:56.696 further DNA damage or they don't
NOTE Confidence: 0.936510996666667
00:22:56.696 --> 00:22:58.040 care about chemo radiotherapy.
NOTE Confidence: 0.893829084
00:23:00.760 --> 00:23:02.600 Now when you summarize these
NOTE Confidence: 0.893829084
00:23:02.600 --> 00:23:06.560 numbers across our glass cohort,
NOTE Confidence: 0.893829084
00:23:06.560 --> 00:23:08.702 we see that amongst IDs wild type
NOTE Confidence: 0.893829084

00:23:08.702 --> 00:23:10.915 tumors that have been treated with
NOTE Confidence: 0.893829084

00:23:10.915 --> 00:23:14.052 temozolomide and or radiation that 15%
NOTE Confidence: 0.893829084

00:23:14.052 --> 00:23:17.036 develops the hypermutation phenotype.
NOTE Confidence: 0.893829084

00:23:17.040 --> 00:23:18.680 And of those that are that do not
NOTE Confidence: 0.893829084

00:23:18.680 --> 00:23:20.239 develop the hypermutation phenotype,
NOTE Confidence: 0.893829084

00:23:20.240 --> 00:23:23.065 another 16% requires large numbers
NOTE Confidence: 0.893829084

00:23:23.065 --> 00:23:26.359 of small deletion which leaves a
NOTE Confidence: 0.893829084

00:23:26.359 --> 00:23:28.959 relatively large group in which no
NOTE Confidence: 0.894589238

00:23:31.080 --> 00:23:32.640 genomic scars can be detected,
NOTE Confidence: 0.894589238

00:23:32.640 --> 00:23:35.472 A recurrence and they may have
NOTE Confidence: 0.894589238

00:23:35.472 --> 00:23:37.760 intrinsic mechanisms to deal with
NOTE Confidence: 0.894589238

00:23:37.760 --> 00:23:39.240 the toxic effects of therapy.
NOTE Confidence: 0.919495188636364

00:23:41.480 --> 00:23:43.202 When we look at IDH mutant
NOTE Confidence: 0.919495188636364

00:23:43.202 --> 00:23:45.051 tumors where the picture is more
NOTE Confidence: 0.919495188636364

00:23:45.051 --> 00:23:46.656 diverse because not all patients
NOTE Confidence: 0.919495188636364

00:23:46.656 --> 00:23:48.519 will receive the same therapies,

NOTE Confidence: 0.919495188636364

00:23:48.520 --> 00:23:50.228 we find that amongst those that have

NOTE Confidence: 0.919495188636364

00:23:50.228 --> 00:23:51.600 been treated with temozolomide,

NOTE Confidence: 0.919495188636364

00:23:51.600 --> 00:23:53.241 42% acquires hypermutation,

NOTE Confidence: 0.919495188636364

00:23:53.241 --> 00:23:55.976 35% of non hypermutators acquires

NOTE Confidence: 0.919495188636364

00:23:55.976 --> 00:23:58.574 the small deletion phenotype and

NOTE Confidence: 0.919495188636364

00:23:58.574 --> 00:24:00.800 again a subset shows neither.

NOTE Confidence: 0.833094546714286

00:24:04.400 --> 00:24:07.024 Now as Jen mentioned in the intro and

NOTE Confidence: 0.833094546714286

00:24:07.024 --> 00:24:09.480 previous work we have looked at gene

NOTE Confidence: 0.833094546714286

00:24:09.480 --> 00:24:11.612 expression patterns and this is focusing

NOTE Confidence: 0.833094546714286

00:24:11.612 --> 00:24:13.915 on GBM so IDH small type tumors.

NOTE Confidence: 0.833094546714286

00:24:13.920 --> 00:24:16.896 And we found that when we evaluate gene

NOTE Confidence: 0.833094546714286

00:24:16.896 --> 00:24:19.690 expression patterns we can and identify 3

NOTE Confidence: 0.833094546714286

00:24:19.690 --> 00:24:21.675 gene expression subtypes of glioblastoma,

NOTE Confidence: 0.833094546714286

00:24:21.680 --> 00:24:23.983 IDH well type glioblastoma which we labeled

NOTE Confidence: 0.833094546714286

00:24:23.983 --> 00:24:25.720 mesenchymal per neural and classical.

NOTE Confidence: 0.810322245

00:24:28.000 --> 00:24:30.634 When we evaluate A subtype classification
NOTE Confidence: 0.810322245

00:24:30.634 --> 00:24:33.702 in glass we see that you know we
NOTE Confidence: 0.810322245

00:24:33.702 --> 00:24:35.328 see the the relative distribution
NOTE Confidence: 0.810322245

00:24:35.328 --> 00:24:37.344 is of these three subtypes is
NOTE Confidence: 0.810322245

00:24:37.344 --> 00:24:39.198 what we typically would expect.
NOTE Confidence: 0.810322245

00:24:39.200 --> 00:24:41.504 A number of cases are classical
NOTE Confidence: 0.810322245

00:24:41.504 --> 00:24:43.882 mesenchymal or per neural at recurrence.
NOTE Confidence: 0.810322245

00:24:43.882 --> 00:24:46.829 We do appear to see a minor
NOTE Confidence: 0.810322245

00:24:46.829 --> 00:24:48.494 shift towards mesenchomal tumor.
NOTE Confidence: 0.810322245

00:24:48.494 --> 00:24:50.630 So we see a high number higher number
NOTE Confidence: 0.810322245

00:24:50.681 --> 00:24:52.396 of mesenchomal tumors and recurrent.
NOTE Confidence: 0.810322245

00:24:52.400 --> 00:24:56.168 So tumor progression appears to
NOTE Confidence: 0.810322245

00:24:56.168 --> 00:24:58.378 and some tumors coincide with
NOTE Confidence: 0.810322245

00:24:58.378 --> 00:24:59.840 mesenchomal transformation.
NOTE Confidence: 0.810322245

00:24:59.840 --> 00:25:01.372 But perhaps more importantly,
NOTE Confidence: 0.810322245

00:25:01.372 --> 00:25:03.670 we find that these subtypes are

NOTE Confidence: 0.810322245

00:25:03.733 --> 00:25:05.680 these subtypes identifications.

NOTE Confidence: 0.810322245

00:25:05.680 --> 00:25:07.184 Classifications are quite flexible

NOTE Confidence: 0.810322245

00:25:07.184 --> 00:25:09.841 because nearly half of our cases actually

NOTE Confidence: 0.810322245

00:25:09.841 --> 00:25:11.551 change subtypes between the initial

NOTE Confidence: 0.810322245

00:25:11.551 --> 00:25:14.160 time point and a recurrent time point.

NOTE Confidence: 0.906012416

00:25:17.080 --> 00:25:18.400 Now, like many tumor types,

NOTE Confidence: 0.906012416

00:25:18.400 --> 00:25:20.380 glioblastoma has been extensively

NOTE Confidence: 0.906012416

00:25:20.380 --> 00:25:22.855 studied using single cell sequencing

NOTE Confidence: 0.906012416

00:25:22.855 --> 00:25:25.160 and single nucleus sequencing.

NOTE Confidence: 0.906012416

00:25:25.160 --> 00:25:27.351 Our collaborator Mario Suva has let let

NOTE Confidence: 0.906012416

00:25:27.351 --> 00:25:29.794 the field in this respect and published

NOTE Confidence: 0.906012416

00:25:29.794 --> 00:25:31.832 a very influential paper in 2019,

NOTE Confidence: 0.906012416

00:25:31.832 --> 00:25:32.760 the Neftal ET al.

NOTE Confidence: 0.906012416

00:25:32.760 --> 00:25:35.545 Study which they found four

NOTE Confidence: 0.906012416

00:25:35.545 --> 00:25:37.773 predominant cell states of

NOTE Confidence: 0.906012416

00:25:37.773 --> 00:25:39.918 glioblastoma which they labeled
NOTE Confidence: 0.906012416

00:25:39.920 --> 00:25:42.480 oligo progenitor cell like neuro,
NOTE Confidence: 0.906012416

00:25:42.480 --> 00:25:44.856 progenital cell like astrocyte
NOTE Confidence: 0.906012416

00:25:44.856 --> 00:25:46.638 like mesenchymol like.
NOTE Confidence: 0.906012416

00:25:46.640 --> 00:25:49.006 You may notice that these terms are
NOTE Confidence: 0.906012416

00:25:49.006 --> 00:25:50.834 actually reminiscent of the subtypes
NOTE Confidence: 0.906012416

00:25:50.834 --> 00:25:52.714 that we had previously identified
NOTE Confidence: 0.906012416

00:25:52.720 --> 00:25:55.320 and that's maybe not surprising.
NOTE Confidence: 0.906012416

00:25:55.320 --> 00:25:57.504 If a tumor contains a majority
NOTE Confidence: 0.906012416

00:25:57.504 --> 00:25:58.596 mesenchymal like cells,
NOTE Confidence: 0.906012416

00:25:58.600 --> 00:26:00.676 the subtype signature will be mesenchymal.
NOTE Confidence: 0.906012416

00:26:00.680 --> 00:26:02.678 We've shown this using combined bulk
NOTE Confidence: 0.906012416

00:26:02.678 --> 00:26:05.398 RNA C and single cell RNA C data sets.
NOTE Confidence: 0.791475449166667

00:26:08.080 --> 00:26:10.789 Oh, and another important thing to remark
NOTE Confidence: 0.791475449166667

00:26:10.789 --> 00:26:13.608 here is that all GBMS each of the cell
NOTE Confidence: 0.791475449166667

00:26:13.608 --> 00:26:15.697 states can be detected in all GBM's.

NOTE Confidence: 0.791475449166667

00:26:15.697 --> 00:26:19.688 It's just a shift in numbers which

NOTE Confidence: 0.791475449166667

00:26:19.688 --> 00:26:21.800 perhaps explains the plasticity

NOTE Confidence: 0.791475449166667

00:26:21.800 --> 00:26:24.440 of expression subtypes over time.

NOTE Confidence: 0.791475449166667

00:26:24.440 --> 00:26:26.547 Now my lab, Kevin and Kevin Johnson

NOTE Confidence: 0.791475449166667

00:26:26.547 --> 00:26:28.476 and Kevin Johnson and Kevin Anderson

NOTE Confidence: 0.791475449166667

00:26:28.476 --> 00:26:30.434 have worked together to do single

NOTE Confidence: 0.791475449166667

00:26:30.434 --> 00:26:32.558 cell sequencing of gliomas as well

NOTE Confidence: 0.791475449166667

00:26:32.560 --> 00:26:35.160 with the purpose of identifying

NOTE Confidence: 0.791475449166667

00:26:35.160 --> 00:26:37.240 pan glioma cell states.

NOTE Confidence: 0.791475449166667

00:26:37.240 --> 00:26:39.004 Mario's Neftal at all cell states

NOTE Confidence: 0.791475449166667

00:26:39.004 --> 00:26:41.198 are focused on IDH well type tumors.

NOTE Confidence: 0.791475449166667

00:26:41.200 --> 00:26:43.380 Our effort initially focused on

NOTE Confidence: 0.791475449166667

00:26:43.380 --> 00:26:45.560 identifying cell states that could

NOTE Confidence: 0.791475449166667

00:26:45.635 --> 00:26:47.375 be identified across different

NOTE Confidence: 0.791475449166667

00:26:47.375 --> 00:26:49.544 types of glioma and we found those

NOTE Confidence: 0.791475449166667

00:26:49.544 --> 00:26:50.840 we labeled them stem like cells,
NOTE Confidence: 0.791475449166667

00:26:50.840 --> 00:26:52.525 proliferating stem like cell and
NOTE Confidence: 0.791475449166667

00:26:52.525 --> 00:26:53.873 differentiated stem like cell.
NOTE Confidence: 0.791475449166667

00:26:53.880 --> 00:26:55.742 And of course with single cell sequencing
NOTE Confidence: 0.791475449166667

00:26:55.742 --> 00:26:57.651 you can also identify non malignant
NOTE Confidence: 0.791475449166667

00:26:57.651 --> 00:26:59.757 cell states such as elutical dendrocytes,
NOTE Confidence: 0.791475449166667

00:26:59.760 --> 00:27:00.117 parasites,
NOTE Confidence: 0.791475449166667

00:27:00.117 --> 00:27:01.188 myeloid cells, cells,
NOTE Confidence: 0.791475449166667

00:27:01.188 --> 00:27:03.330 cells that are typically residing in
NOTE Confidence: 0.791475449166667

00:27:03.390 --> 00:27:05.360 the microenvironment of these gliomas.
NOTE Confidence: 0.768728758666667

00:27:07.760 --> 00:27:10.952 Now you can take, you can infer
NOTE Confidence: 0.768728758666667

00:27:10.952 --> 00:27:13.328 signature gene signatures from these
NOTE Confidence: 0.768728758666667

00:27:13.328 --> 00:27:16.232 single cell States and you can then
NOTE Confidence: 0.768728758666667

00:27:16.232 --> 00:27:18.122 use computational methods to project
NOTE Confidence: 0.768728758666667

00:27:18.122 --> 00:27:20.484 those signatures on bulk RNA C datasets
NOTE Confidence: 0.768728758666667

00:27:20.484 --> 00:27:22.919 such as the ones we have in glass.

NOTE Confidence: 0.768728758666667
00:27:22.920 --> 00:27:26.120 So you can use single cell signatures to
NOTE Confidence: 0.768728758666667
00:27:26.120 --> 00:27:30.720 deconvolute bulk expression profiles.
NOTE Confidence: 0.768728758666667
00:27:30.720 --> 00:27:32.673 So Fred Verne, former post doc in the lab,
NOTE Confidence: 0.768728758666667
00:27:32.680 --> 00:27:35.480 now a faculty member at the Jackson
NOTE Confidence: 0.768728758666667
00:27:35.480 --> 00:27:38.016 laboratory, took this approach,
NOTE Confidence: 0.768728758666667
00:27:38.016 --> 00:27:41.180 used the single cell inferred gene
NOTE Confidence: 0.768728758666667
00:27:41.180 --> 00:27:43.864 signatures from the Kevins and projected
NOTE Confidence: 0.768728758666667
00:27:43.864 --> 00:27:47.640 those onto the glass RNA C data sets.
NOTE Confidence: 0.768728758666667
00:27:47.640 --> 00:27:49.117 This is showing on the left IDH.
NOTE Confidence: 0.768728758666667
00:27:49.120 --> 00:27:51.680 Well the summary of IDH wild type tumors.
NOTE Confidence: 0.768728758666667
00:27:51.680 --> 00:27:54.728 On the right the IDH mutant
NOTE Confidence: 0.768728758666667
00:27:54.728 --> 00:27:56.760 tumors primary and recurrences.
NOTE Confidence: 0.768728758666667
00:27:56.760 --> 00:27:59.154 So when we aggregate all the data,
NOTE Confidence: 0.768728758666667
00:27:59.160 --> 00:28:02.118 first starting with IDH wild types,
NOTE Confidence: 0.768728758666667
00:28:02.120 --> 00:28:05.081 when we aggregate the presence of the
NOTE Confidence: 0.768728758666667

00:28:05.081 --> 00:28:07.788 single cell signatures across the cohort
NOTE Confidence: 0.768728758666667

00:28:07.788 --> 00:28:10.512 and compare initial to recurrent tumors,
NOTE Confidence: 0.768728758666667

00:28:10.520 --> 00:28:13.992 we do not find major shifts in our
NOTE Confidence: 0.768728758666667

00:28:13.992 --> 00:28:18.080 Panvama cell state cell state presence.
NOTE Confidence: 0.768728758666667

00:28:18.080 --> 00:28:20.220 Actually the major difference
NOTE Confidence: 0.768728758666667

00:28:20.220 --> 00:28:22.896 we found when comparing initial
NOTE Confidence: 0.768728758666667

00:28:22.896 --> 00:28:25.768 tumors to recurrent tumors is the
NOTE Confidence: 0.768728758666667

00:28:25.768 --> 00:28:27.224 relative fraction of oligodendrocytes
NOTE Confidence: 0.768728758666667

00:28:27.224 --> 00:28:28.680 in the tumor microenvironment.
NOTE Confidence: 0.817353544285714

00:28:32.360 --> 00:28:35.204 And maybe this is not too
NOTE Confidence: 0.817353544285714

00:28:35.204 --> 00:28:39.073 surprising if you look at the the
NOTE Confidence: 0.817353544285714

00:28:39.073 --> 00:28:41.438 invasive margins of these tumors,
NOTE Confidence: 0.817353544285714

00:28:41.440 --> 00:28:43.036 this is at the time of recurrence.
NOTE Confidence: 0.817353544285714

00:28:43.040 --> 00:28:45.683 This is where most of the tumor cells will
NOTE Confidence: 0.817353544285714

00:28:45.683 --> 00:28:48.023 have come from because this is the area
NOTE Confidence: 0.817353544285714

00:28:48.023 --> 00:28:50.193 of the tumor that's difficult to resect.

NOTE Confidence: 0.817353544285714

00:28:50.200 --> 00:28:52.342 So perhaps at recurrence you can

NOTE Confidence: 0.817353544285714

00:28:52.342 --> 00:28:54.108 imagine that at recurrence more

NOTE Confidence: 0.817353544285714

00:28:54.108 --> 00:28:55.716 of that margin is cut out.

NOTE Confidence: 0.817353544285714

00:28:55.720 --> 00:28:59.200 Therefore, we might be able to see more

NOTE Confidence: 0.817353544285714

00:28:59.200 --> 00:29:00.680 cells from that micro environment,

NOTE Confidence: 0.817353544285714

00:29:00.680 --> 00:29:02.880 in this case particularly oligodendrocytes.

NOTE Confidence: 0.31986508

00:29:05.920 --> 00:29:09.080 What what did seem more surprising

NOTE Confidence: 0.31986508

00:29:09.080 --> 00:29:11.918 to us is then again when Fred used

NOTE Confidence: 0.31986508

00:29:11.918 --> 00:29:13.873 computational methods to not just

NOTE Confidence: 0.31986508

00:29:13.880 --> 00:29:17.809 count enumerate the types of cells in

NOTE Confidence: 0.31986508

00:29:17.809 --> 00:29:19.783 primary to recurrent tumors but also

NOTE Confidence: 0.31986508

00:29:19.783 --> 00:29:22.040 looked at the actual gene expression

NOTE Confidence: 0.31986508

00:29:22.040 --> 00:29:24.921 profile of those cells that we found

NOTE Confidence: 0.31986508

00:29:24.921 --> 00:29:27.056 that a significant increase in

NOTE Confidence: 0.31986508

00:29:27.056 --> 00:29:29.152 neuronal signaling pathways amongst

NOTE Confidence: 0.31986508

00:29:29.152 --> 00:29:31.680 the malignant cell population.
NOTE Confidence: 0.31986508

00:29:31.680 --> 00:29:33.325 Of course you'll find neuronal
NOTE Confidence: 0.31986508

00:29:33.325 --> 00:29:34.641 signaling and oligodendrocytes but
NOTE Confidence: 0.31986508

00:29:34.641 --> 00:29:36.527 what we were finding is that also
NOTE Confidence: 0.31986508

00:29:36.527 --> 00:29:38.840 the malignant cells activate neuronal
NOTE Confidence: 0.31986508

00:29:38.840 --> 00:29:41.960 signaling pathways as recurrence.
NOTE Confidence: 0.31986508

00:29:41.960 --> 00:29:44.552 So we're seeing an increase in
NOTE Confidence: 0.31986508

00:29:44.552 --> 00:29:46.280 oligodendrocytes in the microenvironment
NOTE Confidence: 0.31986508

00:29:46.349 --> 00:29:48.359 but that appears to be converging
NOTE Confidence: 0.31986508

00:29:48.360 --> 00:29:51.000 with increased levels of neuronal
NOTE Confidence: 0.31986508

00:29:51.000 --> 00:29:53.640 signaling by the tumor cells.
NOTE Confidence: 0.31986508

00:29:53.640 --> 00:29:56.520 And when we use a public data set
NOTE Confidence: 0.31986508

00:29:56.520 --> 00:29:59.820 consisting of multi biopsy single cell
NOTE Confidence: 0.31986508

00:29:59.820 --> 00:30:02.800 RNA sequencing from glioblastoma patients,
NOTE Confidence: 0.31986508

00:30:02.800 --> 00:30:05.998 we could again confirm that the
NOTE Confidence: 0.31986508

00:30:05.998 --> 00:30:08.286 malignant single cells expressed

NOTE Confidence: 0.31986508

00:30:08.286 --> 00:30:11.716 higher levels of neuronal pathways

NOTE Confidence: 0.31986508

00:30:11.720 --> 00:30:13.586 when they were when the biopsies

NOTE Confidence: 0.31986508

00:30:13.586 --> 00:30:15.428 were obtained from the margins of

NOTE Confidence: 0.31986508

00:30:15.428 --> 00:30:17.596 the tumor relative to the core of the

NOTE Confidence: 0.31986508

00:30:17.657 --> 00:30:19.589 tumor confirming what Fred had found

NOTE Confidence: 0.31986508

00:30:19.589 --> 00:30:21.520 in our bulk analysis from glass.

NOTE Confidence: 0.8481365

00:30:24.520 --> 00:30:27.236 I'm actually going to skip this one.

NOTE Confidence: 0.8481365

00:30:27.240 --> 00:30:28.962 We decided this to then take

NOTE Confidence: 0.8481365

00:30:28.962 --> 00:30:31.243 this one step further in a large

NOTE Confidence: 0.8481365

00:30:31.243 --> 00:30:33.033 collaboration that involved Mario Suva,

NOTE Confidence: 0.8481365

00:30:33.040 --> 00:30:36.000 Itai, T Rush, Antonio Yavarone,

NOTE Confidence: 0.8481365

00:30:36.000 --> 00:30:38.760 Anna Lazarella as well as many

NOTE Confidence: 0.8481365

00:30:38.760 --> 00:30:40.740 postdoc and junior leads in

NOTE Confidence: 0.8481365

00:30:40.740 --> 00:30:42.720 in in these respective labs.

NOTE Confidence: 0.8481365

00:30:42.720 --> 00:30:43.844 Collaborating with MD Anderson,

NOTE Confidence: 0.8481365

00:30:43.844 --> 00:30:45.530 Duke and a number a number
NOTE Confidence: 0.8481365

00:30:45.582 --> 00:30:46.599 of other institutions
NOTE Confidence: 0.718076270526316

00:30:49.800 --> 00:30:51.965 we acquired. We generated longitudinal
NOTE Confidence: 0.718076270526316

00:30:51.965 --> 00:30:55.280 single nucleus RNA seed data for a large
NOTE Confidence: 0.718076270526316

00:30:55.280 --> 00:30:57.434 number of IDH wild type glioblastomas,
NOTE Confidence: 0.718076270526316

00:30:57.440 --> 00:30:59.736 again in the context of annotation for
NOTE Confidence: 0.718076270526316

00:30:59.736 --> 00:31:02.122 different types of therapy and we also
NOTE Confidence: 0.718076270526316

00:31:02.122 --> 00:31:04.126 were able to generate exomorphol genome
NOTE Confidence: 0.718076270526316

00:31:04.190 --> 00:31:06.437 sequencing on the majority of our core.
NOTE Confidence: 0.903100802

00:31:08.920 --> 00:31:13.640 So previously Mario and colleagues
NOTE Confidence: 0.903100802

00:31:13.640 --> 00:31:16.440 identified these four cell states that I
NOTE Confidence: 0.903100802

00:31:16.440 --> 00:31:21.000 mentioned earlier, NPCOPCACMS like cells.
NOTE Confidence: 0.903100802

00:31:21.000 --> 00:31:24.360 When we analyzed over 500,000 cells from
NOTE Confidence: 0.903100802

00:31:24.360 --> 00:31:28.176 this cohort and again to derive cell states
NOTE Confidence: 0.903100802

00:31:28.176 --> 00:31:31.319 as well as transcriptional meta programs,
NOTE Confidence: 0.903100802

00:31:31.320 --> 00:31:33.990 we find these same 4 cell States and the gene

NOTE Confidence: 0.903100802

00:31:34.050 --> 00:31:36.717 express's check features that come from them.

NOTE Confidence: 0.903100802

00:31:36.720 --> 00:31:40.168 Again, here is OPC, AC,

NOTE Confidence: 0.903100802

00:31:40.168 --> 00:31:41.296 mesenchymal, and NPC.

NOTE Confidence: 0.903100802

00:31:41.296 --> 00:31:43.872 But of course we found many more

NOTE Confidence: 0.903100802

00:31:43.872 --> 00:31:46.200 because of the much larger cohort

NOTE Confidence: 0.903100802

00:31:46.200 --> 00:31:48.097 as well as because in his Mario's

NOTE Confidence: 0.903100802

00:31:48.097 --> 00:31:49.998 initial study he had only untreated,

NOTE Confidence: 0.903100802

00:31:50.000 --> 00:31:51.480 he included only untreated tumors.

NOTE Confidence: 0.903100802

00:31:51.480 --> 00:31:53.545 And now we're looking at

NOTE Confidence: 0.903100802

00:31:53.545 --> 00:31:55.097 both primary and recurrences.

NOTE Confidence: 0.903100802

00:31:55.097 --> 00:31:57.371 So our large data set enabled

NOTE Confidence: 0.903100802

00:31:57.371 --> 00:31:59.479 us to find the number of new

NOTE Confidence: 0.903100802

00:31:59.480 --> 00:32:01.360 glioblastoma related cell programs.

NOTE Confidence: 0.9436683

00:32:06.040 --> 00:32:08.505 As we had also observed

NOTE Confidence: 0.9436683

00:32:08.505 --> 00:32:10.477 in our glass analysis,

NOTE Confidence: 0.9436683

00:32:10.480 --> 00:32:12.680 the relative number of malignant
NOTE Confidence: 0.9436683

00:32:12.680 --> 00:32:14.440 cells decreased at recurrence.
NOTE Confidence: 0.9436683

00:32:14.440 --> 00:32:16.915 So recurrent GBMS become less
NOTE Confidence: 0.9436683

00:32:16.915 --> 00:32:19.536 pure or more incorporate more
NOTE Confidence: 0.9436683

00:32:19.536 --> 00:32:21.240 tumor microenvironment cells.
NOTE Confidence: 0.9436683

00:32:21.240 --> 00:32:23.528 So we see a decrease in the number
NOTE Confidence: 0.9436683

00:32:23.528 --> 00:32:25.239 of proportion of malignant cells
NOTE Confidence: 0.9436683

00:32:25.240 --> 00:32:26.962 and an increase and we confirmed
NOTE Confidence: 0.9436683

00:32:26.962 --> 00:32:29.121 the increase in the number of
NOTE Confidence: 0.9436683

00:32:29.121 --> 00:32:30.353 oligodendrocytes that's because of
NOTE Confidence: 0.9436683

00:32:30.353 --> 00:32:31.859 the greater resolution of the single
NOTE Confidence: 0.9436683

00:32:31.859 --> 00:32:33.478 cell of the new single nucleus data.
NOTE Confidence: 0.9436683

00:32:33.480 --> 00:32:34.974 We also see a significant increase
NOTE Confidence: 0.9436683

00:32:34.974 --> 00:32:36.611 in the number of astrocytes in
NOTE Confidence: 0.9436683

00:32:36.611 --> 00:32:38.076 the number of neuronal cells
NOTE Confidence: 0.807201150588235

00:32:42.200 --> 00:32:44.696 converging with the result from glass

NOTE Confidence: 0.807201150588235
00:32:44.696 --> 00:32:47.424 that most tumors or many tumors
NOTE Confidence: 0.807201150588235
00:32:47.424 --> 00:32:49.879 change tumor subtype at recurrence.
NOTE Confidence: 0.807201150588235
00:32:49.880 --> 00:32:54.062 We find large shifts in cell states
NOTE Confidence: 0.807201150588235
00:32:54.062 --> 00:32:57.317 between primary and recurrent tumors
NOTE Confidence: 0.807201150588235
00:32:57.320 --> 00:33:00.216 and the one that maybe is interesting is
NOTE Confidence: 0.807201150588235
00:33:00.216 --> 00:33:02.960 hypoxia and I'll get back to that later.
NOTE Confidence: 0.807201150588235
00:33:02.960 --> 00:33:06.576 So a subset of this smaller color compared
NOTE Confidence: 0.807201150588235
00:33:06.576 --> 00:33:08.724 to glass acquired this small deletion
NOTE Confidence: 0.807201150588235
00:33:08.724 --> 00:33:10.279 phenotype that I mentioned earlier.
NOTE Confidence: 0.807201150588235
00:33:10.280 --> 00:33:14.456 In fact 10 of 46 tumors where we had
NOTE Confidence: 0.807201150588235
00:33:14.456 --> 00:33:16.976 converging DNA sequencing and single
NOTE Confidence: 0.807201150588235
00:33:16.976 --> 00:33:19.410 nucleus sequencing data acquired this
NOTE Confidence: 0.807201150588235
00:33:19.410 --> 00:33:22.080 small deletion phenotype as shown here.
NOTE Confidence: 0.807201150588235
00:33:22.080 --> 00:33:25.014 And what we're seeing is that when a small
NOTE Confidence: 0.807201150588235
00:33:25.014 --> 00:33:27.200 deletion phenotype has been acquired,
NOTE Confidence: 0.807201150588235

00:33:27.200 --> 00:33:28.586 tumors will increase.
NOTE Confidence: 0.807201150588235

00:33:28.586 --> 00:33:32.120 We find that more tumor cells show signs
NOTE Confidence: 0.807201150588235

00:33:32.120 --> 00:33:34.400 of hypoxia are responding to hypoxia.
NOTE Confidence: 0.8566362025

00:33:37.080 --> 00:33:41.529 So radiation either drives or
NOTE Confidence: 0.8566362025

00:33:41.529 --> 00:33:43.574 shows its most significant effects
NOTE Confidence: 0.8566362025

00:33:43.574 --> 00:33:46.079 in cells in regions of hypoxia.
NOTE Confidence: 0.738392116

00:33:50.120 --> 00:33:52.200 When we then went back to our glass
NOTE Confidence: 0.738392116

00:33:52.200 --> 00:33:53.856 data sets, we could confirm that
NOTE Confidence: 0.738392116

00:33:53.856 --> 00:33:55.560 indeed tumors that acquire lots of
NOTE Confidence: 0.738392116

00:33:55.612 --> 00:33:57.282 small deletions are also showing
NOTE Confidence: 0.738392116

00:33:57.282 --> 00:33:58.952 an increase in hypoxic signaling,
NOTE Confidence: 0.738392116

00:33:58.960 --> 00:34:01.360 hypoxia cell state signaling compared to
NOTE Confidence: 0.738392116

00:34:01.360 --> 00:34:04.600 tumors that do not acquire small deletion.
NOTE Confidence: 0.893243085833333

00:34:07.200 --> 00:34:08.905 This is potentially relevant because
NOTE Confidence: 0.893243085833333

00:34:08.905 --> 00:34:10.933 hypoxia is a phenomenon you can
NOTE Confidence: 0.893243085833333

00:34:10.933 --> 00:34:13.560 detect through imaging and of course

NOTE Confidence: 0.893243085833333
00:34:13.560 --> 00:34:15.920 these results built upon large
NOTE Confidence: 0.893243085833333
00:34:15.920 --> 00:34:18.480 and large amount of literature
NOTE Confidence: 0.893243085833333
00:34:18.480 --> 00:34:20.100 demonstrating the convergence of
NOTE Confidence: 0.893243085833333
00:34:20.100 --> 00:34:21.720 radiation response with hypoxia.
NOTE Confidence: 0.934327004285714
00:34:25.960 --> 00:34:27.536 We then also focused,
NOTE Confidence: 0.934327004285714
00:34:27.536 --> 00:34:29.752 we then also performed A comparable
NOTE Confidence: 0.934327004285714
00:34:29.752 --> 00:34:32.160 analysis but looking at IDH mutant tumor.
NOTE Confidence: 0.934327004285714
00:34:32.160 --> 00:34:34.440 So we generated single nucleus
NOTE Confidence: 0.934327004285714
00:34:34.440 --> 00:34:37.560 RNA CC data on IDH mutants,
NOTE Confidence: 0.934327004285714
00:34:37.560 --> 00:34:39.664 a cohort of 35 cases and this is
NOTE Confidence: 0.934327004285714
00:34:39.664 --> 00:34:42.230 work led by Kevin Johnson who is a
NOTE Confidence: 0.934327004285714
00:34:42.230 --> 00:34:44.490 research scientist in our lab again
NOTE Confidence: 0.934327004285714
00:34:44.490 --> 00:34:47.680 with the same collaborator team.
NOTE Confidence: 0.722302904545455
00:34:51.400 --> 00:34:53.895 Mario Nita's labs have previously
NOTE Confidence: 0.722302904545455
00:34:53.895 --> 00:34:57.520 found that in IDH mutant tumors they
NOTE Confidence: 0.722302904545455

00:34:57.520 --> 00:35:00.506 they found less consistent cell cell
NOTE Confidence: 0.722302904545455

00:35:00.506 --> 00:35:02.436 state and gene expression programs.
NOTE Confidence: 0.722302904545455

00:35:02.440 --> 00:35:05.944 But they found that all that most tumors
NOTE Confidence: 0.722302904545455

00:35:05.944 --> 00:35:09.666 could be projected along an axis of stem
NOTE Confidence: 0.722302904545455

00:35:09.666 --> 00:35:13.560 like to stem like Sigma from stem like
NOTE Confidence: 0.722302904545455

00:35:13.560 --> 00:35:16.674 states to a more differentiated state.
NOTE Confidence: 0.722302904545455

00:35:16.680 --> 00:35:19.956 Because IDH mutant tumors in general are
NOTE Confidence: 0.722302904545455

00:35:19.956 --> 00:35:22.800 either astrocytoma or oligodendrocyte glioma,
NOTE Confidence: 0.722302904545455

00:35:22.800 --> 00:35:25.440 They showed that astrocyte
NOTE Confidence: 0.794522625714286

00:35:27.520 --> 00:35:29.400 IDH mutant gliomas differentiate
NOTE Confidence: 0.794522625714286

00:35:29.400 --> 00:35:33.173 from a stem like cell to a astrocyte
NOTE Confidence: 0.794522625714286

00:35:33.173 --> 00:35:34.864 like cell phenotype whereas
NOTE Confidence: 0.794522625714286

00:35:34.864 --> 00:35:37.336 oligodendrocytes go from a stem like
NOTE Confidence: 0.794522625714286

00:35:37.336 --> 00:35:39.931 state to a more oligodendrocyte like
NOTE Confidence: 0.794522625714286

00:35:39.931 --> 00:35:41.482 state as potentially expected.
NOTE Confidence: 0.794522625714286

00:35:41.482 --> 00:35:44.464 So the non coders go to the left

NOTE Confidence: 0.794522625714286
00:35:44.464 --> 00:35:48.040 and the codels go to the right.
NOTE Confidence: 0.794522625714286
00:35:48.040 --> 00:35:50.080 In our paper from 2022 with
NOTE Confidence: 0.794522625714286
00:35:50.080 --> 00:35:51.440 Fred as first author,
NOTE Confidence: 0.794522625714286
00:35:51.440 --> 00:35:56.158 we had noticed that amongst IDH mutants
NOTE Confidence: 0.794522625714286
00:35:56.160 --> 00:35:59.160 those that show signs of treatment
NOTE Confidence: 0.794522625714286
00:35:59.160 --> 00:36:01.160 response either through hypermutation
NOTE Confidence: 0.794522625714286
00:36:01.160 --> 00:36:04.275 or through acquired sydicand to a loss,
NOTE Confidence: 0.794522625714286
00:36:04.280 --> 00:36:07.108 we saw an increase in the proportion
NOTE Confidence: 0.794522625714286
00:36:07.108 --> 00:36:09.002 of proliferating stem like cells
NOTE Confidence: 0.794522625714286
00:36:09.002 --> 00:36:11.555 which would be in the in the trunk
NOTE Confidence: 0.794522625714286
00:36:11.555 --> 00:36:14.600 of the axis shown on the left.
NOTE Confidence: 0.794522625714286
00:36:14.600 --> 00:36:17.496 So we took those results and we
NOTE Confidence: 0.794522625714286
00:36:17.496 --> 00:36:19.136 took those into consideration as
NOTE Confidence: 0.794522625714286
00:36:19.136 --> 00:36:21.360 we started to analyze these data.
NOTE Confidence: 0.794522625714286
00:36:21.360 --> 00:36:23.670 So first we Kevin generated these U
NOTE Confidence: 0.794522625714286

00:36:23.670 --> 00:36:26.280 maps that you can see in many papers.
NOTE Confidence: 0.794522625714286

00:36:26.280 --> 00:36:28.410 We had generated data from large
NOTE Confidence: 0.794522625714286

00:36:28.410 --> 00:36:29.475 numbers of nuclei,
NOTE Confidence: 0.794522625714286

00:36:29.480 --> 00:36:32.416 I would say quite unprecedented to show
NOTE Confidence: 0.794522625714286

00:36:32.416 --> 00:36:35.244 that you can infer your typical sets
NOTE Confidence: 0.794522625714286

00:36:35.244 --> 00:36:37.880 of cell state programs as shown here.
NOTE Confidence: 0.794522625714286

00:36:37.880 --> 00:36:39.896 So we have now generated a very
NOTE Confidence: 0.794522625714286

00:36:39.896 --> 00:36:42.222 large number of IDH smooth and single
NOTE Confidence: 0.794522625714286

00:36:42.222 --> 00:36:44.665 nucleus data and through that we can
NOTE Confidence: 0.794522625714286

00:36:44.665 --> 00:36:47.441 create a definition of cell States and
NOTE Confidence: 0.794522625714286

00:36:47.441 --> 00:36:50.315 associated metaprograms of IDH mutant tumors.
NOTE Confidence: 0.794522625714286

00:36:50.320 --> 00:36:54.328 And the metaprograms we arrived at
NOTE Confidence: 0.794522625714286

00:36:54.328 --> 00:36:56.215 actually are quite reminiscent of those
NOTE Confidence: 0.794522625714286

00:36:56.215 --> 00:36:58.278 that are shown in IDH wild type tumors.
NOTE Confidence: 0.685008754285714

00:37:02.920 --> 00:37:05.195 Interestingly, when we looked at the this,
NOTE Confidence: 0.685008754285714

00:37:05.200 --> 00:37:08.648 when we projected the 35 cases that we

NOTE Confidence: 0.685008754285714
00:37:08.648 --> 00:37:11.280 had analyzed that we had sequenced,
NOTE Confidence: 0.685008754285714
00:37:11.280 --> 00:37:13.152 we projected them on that same
NOTE Confidence: 0.685008754285714
00:37:13.152 --> 00:37:16.192 inferred Y axis as Mario and Itai had
NOTE Confidence: 0.685008754285714
00:37:16.192 --> 00:37:18.432 previously used in their analysis.
NOTE Confidence: 0.685008754285714
00:37:18.440 --> 00:37:19.994 We see that tumors tend to shift.
NOTE Confidence: 0.685008754285714
00:37:20.000 --> 00:37:21.450 So there's the circles here
NOTE Confidence: 0.685008754285714
00:37:21.450 --> 00:37:23.120 are the initial tumors and the
NOTE Confidence: 0.685008754285714
00:37:23.120 --> 00:37:25.680 triangles are the recurrent tumors.
NOTE Confidence: 0.685008754285714
00:37:25.680 --> 00:37:28.476 We see that nearly all tumors
NOTE Confidence: 0.685008754285714
00:37:28.480 --> 00:37:31.400 shift into an upward direction.
NOTE Confidence: 0.685008754285714
00:37:31.400 --> 00:37:34.235 So the relative amount of stem like or stem,
NOTE Confidence: 0.685008754285714
00:37:34.240 --> 00:37:36.340 the relative amount of stemness
NOTE Confidence: 0.685008754285714
00:37:36.340 --> 00:37:38.944 in these tumors almost universally
NOTE Confidence: 0.685008754285714
00:37:38.944 --> 00:37:40.960 increases upon recurrence.
NOTE Confidence: 0.685008754285714
00:37:40.960 --> 00:37:42.916 So tumor seems to de differentiate
NOTE Confidence: 0.863617665714286

00:37:46.680 --> 00:37:48.556 as a part of their tumor progression.
NOTE Confidence: 0.898238688

00:37:52.520 --> 00:37:53.560 This is also shown here.
NOTE Confidence: 0.898238688

00:37:53.560 --> 00:37:56.728 These are different some of the different
NOTE Confidence: 0.898238688

00:37:56.728 --> 00:37:59.040 meta programs that we had arrived at
NOTE Confidence: 0.898238688

00:37:59.040 --> 00:38:01.480 looking at different grades amongst
NOTE Confidence: 0.898238688

00:38:01.480 --> 00:38:05.030 Codells and non Codells and we see
NOTE Confidence: 0.898238688

00:38:05.030 --> 00:38:06.940 that a differentiated differentiation
NOTE Confidence: 0.898238688

00:38:06.940 --> 00:38:10.160 cell state such as the AC like
NOTE Confidence: 0.898238688

00:38:10.235 --> 00:38:12.372 state decreases upon with grade.
NOTE Confidence: 0.898238688

00:38:12.372 --> 00:38:15.864 And that's true for both Codells and non
NOTE Confidence: 0.898238688

00:38:15.864 --> 00:38:18.172 Codells whereas undifferentiated and
NOTE Confidence: 0.898238688

00:38:18.172 --> 00:38:22.680 number of cycling cells increases with grade.
NOTE Confidence: 0.898238688

00:38:22.680 --> 00:38:26.676 And when we actually pair up the tumor,
NOTE Confidence: 0.898238688

00:38:26.680 --> 00:38:28.885 so not split them by grade but
NOTE Confidence: 0.898238688

00:38:28.885 --> 00:38:30.839 actually look at paired samples
NOTE Confidence: 0.898238688

00:38:30.840 --> 00:38:34.116 again we confirm that the amount of

NOTE Confidence: 0.898238688

00:38:34.116 --> 00:38:35.520 undifferentiated cells increases,

NOTE Confidence: 0.898238688

00:38:35.520 --> 00:38:38.280 the amount of cycling cells increases,

NOTE Confidence: 0.898238688

00:38:38.280 --> 00:38:41.010 cells that show signs of stress increases

NOTE Confidence: 0.898238688

00:38:41.010 --> 00:38:43.245 in proportion and finally mesenchymal

NOTE Confidence: 0.898238688

00:38:43.245 --> 00:38:45.440 like cells increase in proportion.

NOTE Confidence: 0.9731241

00:38:48.520 --> 00:38:52.948 Now what is in my view most interesting

NOTE Confidence: 0.9731241

00:38:52.948 --> 00:38:55.788 about these observations is when we now

NOTE Confidence: 0.9731241

00:38:55.788 --> 00:38:58.230 separate our you know relatively modest

NOTE Confidence: 0.9731241

00:38:58.312 --> 00:39:02.400 cohort but still into cases that have signs

NOTE Confidence: 0.9731241

00:39:02.400 --> 00:39:05.280 of therapy induced genetic alterations.

NOTE Confidence: 0.9731241

00:39:05.280 --> 00:39:07.023 But those are the ones that also

NOTE Confidence: 0.9731241

00:39:07.023 --> 00:39:09.478 are also those are the ones that are

NOTE Confidence: 0.9731241

00:39:09.478 --> 00:39:10.798 driving these significant changes.

NOTE Confidence: 0.9731241

00:39:10.800 --> 00:39:14.590 So tumors that do not reflect therapy induced

NOTE Confidence: 0.9731241

00:39:14.590 --> 00:39:17.040 genetic alterations such as hypermutation,

NOTE Confidence: 0.9731241

00:39:17.040 --> 00:39:20.488 citic anti a loss or loss of new
NOTE Confidence: 0.9731241

00:39:20.488 --> 00:39:22.240 aneuploidies, we find no significant
NOTE Confidence: 0.9731241

00:39:22.240 --> 00:39:23.560 difference in cell states.
NOTE Confidence: 0.9731241

00:39:23.560 --> 00:39:26.514 It's only those tumors that show a
NOTE Confidence: 0.9731241

00:39:26.514 --> 00:39:28.179 treatment induced alteration that
NOTE Confidence: 0.9731241

00:39:28.179 --> 00:39:30.475 are the ones that also show changes
NOTE Confidence: 0.9731241

00:39:30.475 --> 00:39:32.878 in their gene expression programs.
NOTE Confidence: 0.860788142

00:39:35.960 --> 00:39:38.893 So to then re annotate the
NOTE Confidence: 0.860788142

00:39:38.893 --> 00:39:42.158 flow charts I showed earlier,
NOTE Confidence: 0.860788142

00:39:42.160 --> 00:39:44.044 we're seeing that subsets of IDH
NOTE Confidence: 0.860788142

00:39:44.044 --> 00:39:46.556 mutant as well as IDH wild type
NOTE Confidence: 0.860788142

00:39:46.556 --> 00:39:48.140 tumors acquire genetic alterations
NOTE Confidence: 0.860788142

00:39:48.140 --> 00:39:50.720 in response to treatment and we're
NOTE Confidence: 0.860788142

00:39:50.720 --> 00:39:53.000 now finding using our bulk and
NOTE Confidence: 0.860788142

00:39:53.000 --> 00:39:54.800 single nucleus our expression
NOTE Confidence: 0.860788142

00:39:54.800 --> 00:39:56.844 gene expression datasets that

NOTE Confidence: 0.860788142

00:39:56.844 --> 00:39:59.399 this coincides with increased cell

NOTE Confidence: 0.860788142

00:39:59.399 --> 00:40:01.958 cycle activity and proliferation.

NOTE Confidence: 0.860788142

00:40:01.960 --> 00:40:04.400 And D differentiation programs

NOTE Confidence: 0.860788142

00:40:04.400 --> 00:40:07.866 and IDH mutant glomus but with

NOTE Confidence: 0.860788142

00:40:07.866 --> 00:40:09.918 neuronal and mesenchomal signaling

NOTE Confidence: 0.860788142

00:40:09.918 --> 00:40:13.000 activity and IDH wild type tumors.

NOTE Confidence: 0.860788142

00:40:13.000 --> 00:40:16.680 So it leads me to summarize at the end here.

NOTE Confidence: 0.860788142

00:40:16.680 --> 00:40:19.576 IDH wild type gliomas so far seem to

NOTE Confidence: 0.860788142

00:40:19.576 --> 00:40:21.675 undergo tumor cell extrinsic changes

NOTE Confidence: 0.860788142

00:40:21.675 --> 00:40:24.713 which sets them apart from IDH mutant

NOTE Confidence: 0.860788142

00:40:24.790 --> 00:40:27.484 glomas which appear to a majority

NOTE Confidence: 0.860788142

00:40:27.484 --> 00:40:29.673 undergo tumor cell intrinsic transitions,

NOTE Confidence: 0.860788142

00:40:29.673 --> 00:40:32.040 which I think is a peculiar

NOTE Confidence: 0.860788142

00:40:32.040 --> 00:40:33.240 but interesting difference

NOTE Confidence: 0.934605338

00:40:35.400 --> 00:40:37.800 As we think about developing new

NOTE Confidence: 0.934605338

00:40:37.800 --> 00:40:39.400 therapies for these patients,
NOTE Confidence: 0.934605338

00:40:39.400 --> 00:40:42.760 this is something to take into consideration.
NOTE Confidence: 0.934605338

00:40:42.760 --> 00:40:46.680 And finally amongst the IDH mutant gliomas,
NOTE Confidence: 0.934605338

00:40:46.680 --> 00:40:49.256 the changes we are observing are mostly
NOTE Confidence: 0.934605338

00:40:49.256 --> 00:40:52.000 observed when in those tumors that have
NOTE Confidence: 0.934605338

00:40:52.000 --> 00:40:54.736 been treated and we find convergence
NOTE Confidence: 0.934605338

00:40:54.736 --> 00:40:56.672 between newly acquired genetic
NOTE Confidence: 0.934605338

00:40:56.672 --> 00:40:58.968 alterations with cell state transitions.
NOTE Confidence: 0.934605338

00:40:58.968 --> 00:41:01.680 So that leads to the question,
NOTE Confidence: 0.934605338

00:41:01.680 --> 00:41:04.060 are these tumors changing because
NOTE Confidence: 0.934605338

00:41:04.060 --> 00:41:06.867 of the treatment or are the
NOTE Confidence: 0.934605338

00:41:06.867 --> 00:41:09.002 oncologists treating the tumors that
NOTE Confidence: 0.934605338

00:41:09.002 --> 00:41:11.878 are more likely to change or both?
NOTE Confidence: 0.934605338

00:41:11.880 --> 00:41:15.360 That's something for a next analysis.
NOTE Confidence: 0.934605338

00:41:15.360 --> 00:41:17.075 With that, I come to the end,
NOTE Confidence: 0.934605338

00:41:17.080 --> 00:41:18.676 I'd like to thank all the people

NOTE Confidence: 0.934605338

00:41:18.676 --> 00:41:20.549 in the lab that worked very hard

NOTE Confidence: 0.934605338

00:41:20.549 --> 00:41:22.241 for these results and of course

NOTE Confidence: 0.934605338

00:41:22.295 --> 00:41:23.506 our funding our funders.

NOTE Confidence: 0.934605338

00:41:23.506 --> 00:41:24.758 Thank you very much.

NOTE Confidence: 0.802829375555556

00:41:29.120 --> 00:41:31.280 Thank you. Jen had to run to the OR,

NOTE Confidence: 0.802829375555556

00:41:31.280 --> 00:41:33.320 so I will handle the questions.

NOTE Confidence: 0.802829375555556

00:41:33.320 --> 00:41:34.290 Do we have any questions

NOTE Confidence: 0.802829375555556

00:41:34.290 --> 00:41:37.998 from the room or online?

NOTE Confidence: 0.802829375555556

00:41:38.000 --> 00:41:39.580 You mentioned immunotherapy,

NOTE Confidence: 0.802829375555556

00:41:39.580 --> 00:41:42.088 so are there protocols now that

NOTE Confidence: 0.802829375555556

00:41:42.088 --> 00:41:43.516 are using some of these markers to

NOTE Confidence: 0.802829375555556

00:41:43.516 --> 00:41:44.688 determine who should get immunotherapy

NOTE Confidence: 0.802829375555556

00:41:44.688 --> 00:41:46.074 and which ones in this disease.

NOTE Confidence: 0.820231249

00:41:46.400 --> 00:41:48.200 So regrettably all the results so

NOTE Confidence: 0.820231249

00:41:48.200 --> 00:41:49.973 far I've shown that checkpoint

NOTE Confidence: 0.820231249

00:41:49.973 --> 00:41:52.838 inhibition does relative does little
NOTE Confidence: 0.820231249

00:41:52.838 --> 00:41:55.559 for these patients and that's likely
NOTE Confidence: 0.820231249

00:41:55.559 --> 00:41:57.224 because of the very immunosuppressive
NOTE Confidence: 0.820231249

00:41:57.224 --> 00:41:58.520 microenvironment in these tumors.
NOTE Confidence: 0.820231249

00:41:58.520 --> 00:42:00.440 There's very few active T cells.
NOTE Confidence: 0.820231249

00:42:00.440 --> 00:42:02.169 So you can treat them at checkpoint
NOTE Confidence: 0.820231249

00:42:02.169 --> 00:42:03.570 inhibition but without T cells that's
NOTE Confidence: 0.820231249

00:42:03.570 --> 00:42:06.800 going to not really result in any benefit.
NOTE Confidence: 0.820231249

00:42:06.800 --> 00:42:09.460 So moving forward the way to get
NOTE Confidence: 0.820231249

00:42:09.460 --> 00:42:11.649 immunotherapies to work in these patients
NOTE Confidence: 0.820231249

00:42:11.649 --> 00:42:14.583 would be to figure out how can we get
NOTE Confidence: 0.820231249

00:42:14.583 --> 00:42:16.919 T cells into the tumor and only then
NOTE Confidence: 0.820231249

00:42:16.920 --> 00:42:19.400 immunotherapy is is likely to have a chance.
NOTE Confidence: 0.820231249

00:42:19.400 --> 00:42:20.096 Got it. OK.
NOTE Confidence: 0.820231249

00:42:20.096 --> 00:42:21.433 Any questions in the room? OK.
NOTE Confidence: 0.820231249

00:42:21.433 --> 00:42:22.826 I will walk the microphone around.

NOTE Confidence: 0.820231249

00:42:22.826 --> 00:42:24.760 I'll go the front row here first.

NOTE Confidence: 0.864485463846154

00:42:27.520 --> 00:42:30.404 Hello. Oh thanks. A beautiful talk and

NOTE Confidence: 0.864485463846154

00:42:30.404 --> 00:42:33.090 I think you know just to it's something

NOTE Confidence: 0.864485463846154

00:42:33.090 --> 00:42:36.520 that we are all hoping to be able to

NOTE Confidence: 0.864485463846154

00:42:36.520 --> 00:42:38.640 replicate in different tumor types.

NOTE Confidence: 0.79730321625

00:42:40.160 --> 00:42:42.280 What a what a great example of a

NOTE Confidence: 0.79730321625

00:42:42.280 --> 00:42:44.680 a treasure trove of information.

NOTE Confidence: 0.79730321625

00:42:44.680 --> 00:42:47.240 My question is about epigenetic regulation

NOTE Confidence: 0.964317662

00:42:47.240 --> 00:42:50.000 and I saw one slide with EZH 2

NOTE Confidence: 0.964317662

00:42:50.000 --> 00:42:52.160 your thoughts or if you've looked

NOTE Confidence: 0.964317662

00:42:52.160 --> 00:42:55.440 at sort of wrapping of chromatin

NOTE Confidence: 0.964317662

00:42:55.440 --> 00:42:57.680 epigenetic regulation specifically

NOTE Confidence: 0.964317662

00:42:57.680 --> 00:42:59.680 after radiation, if that's changed,

NOTE Confidence: 0.964317662

00:42:59.680 --> 00:43:01.960 if we can explore that with some of our,

NOTE Confidence: 0.964317662

00:43:01.960 --> 00:43:02.872 for example, ECH,

NOTE Confidence: 0.964317662

00:43:02.872 --> 00:43:04.839 two or other regulators there,
NOTE Confidence: 0.964317662

00:43:04.840 --> 00:43:06.040 inhibitors there,
NOTE Confidence: 0.89859699

00:43:08.000 --> 00:43:10.720 that's a great question.
NOTE Confidence: 0.89859699

00:43:10.720 --> 00:43:12.760 So just from a data perspective,
NOTE Confidence: 0.89859699

00:43:12.760 --> 00:43:15.136 we have been able to collect
NOTE Confidence: 0.89859699

00:43:15.136 --> 00:43:16.720 the NMS elation profiles,
NOTE Confidence: 0.89859699

00:43:16.720 --> 00:43:18.640 other members of the glass
NOTE Confidence: 0.89859699

00:43:18.640 --> 00:43:20.560 consortium have looked at those.
NOTE Confidence: 0.89859699

00:43:20.560 --> 00:43:22.792 What we see in the IDH wild type tumors,
NOTE Confidence: 0.89859699

00:43:22.800 --> 00:43:25.092 we don't see many changes from
NOTE Confidence: 0.89859699

00:43:25.092 --> 00:43:28.198 a Dena methylation perspective.
NOTE Confidence: 0.89859699

00:43:28.200 --> 00:43:29.920 These tumors have lots of things going on,
NOTE Confidence: 0.89859699

00:43:29.920 --> 00:43:32.237 but it doesn't really seem to change
NOTE Confidence: 0.89859699

00:43:32.237 --> 00:43:34.130 in directly their DNA methylation
NOTE Confidence: 0.89859699

00:43:34.130 --> 00:43:35.899 profile and the IDH mutants.
NOTE Confidence: 0.89859699

00:43:35.899 --> 00:43:38.492 We see that the subset of tumors goes

NOTE Confidence: 0.89859699

00:43:38.492 --> 00:43:40.940 from a relatively high amount of genome

NOTE Confidence: 0.89859699

00:43:40.940 --> 00:43:43.880 Y DNA methylation to a decreased amount.

NOTE Confidence: 0.89859699

00:43:43.880 --> 00:43:45.644 So and those are the ones that

NOTE Confidence: 0.89859699

00:43:45.644 --> 00:43:47.955 also are also the ones that change

NOTE Confidence: 0.89859699

00:43:47.955 --> 00:43:49.447 that acquire genetic alterations

NOTE Confidence: 0.89859699

00:43:49.447 --> 00:43:51.398 that change cell state programs,

NOTE Confidence: 0.89859699

00:43:51.400 --> 00:43:54.904 those also seem to demethylate or

NOTE Confidence: 0.89859699

00:43:54.904 --> 00:43:57.240 show demethylation genome wide.

NOTE Confidence: 0.89859699

00:43:57.240 --> 00:43:58.905 Now whether that has implications

NOTE Confidence: 0.89859699

00:43:58.905 --> 00:44:00.916 for treatment with ECH 2 inhibitors

NOTE Confidence: 0.89859699

00:44:00.916 --> 00:44:02.876 would be a bit of a stretch.

NOTE Confidence: 0.89859699

00:44:02.880 --> 00:44:06.555 I know those are being considered for

NOTE Confidence: 0.89859699

00:44:06.560 --> 00:44:10.080 the H3 wild type pediatric GBMS for example,

NOTE Confidence: 0.873603212307692

00:44:12.120 --> 00:44:13.920 but right now I don't have information on

NOTE Confidence: 0.873603212307692

00:44:13.920 --> 00:44:15.560 whether that will work for for adults.

NOTE Confidence: 0.5595026383333333

00:44:17.240 --> 00:44:18.116 Great, we can go to Doctor
NOTE Confidence: 0.5595026383333333

00:44:18.120 --> 00:44:19.320 crop and then doctor Contessa
NOTE Confidence: 0.5595026383333333

00:44:19.320 --> 00:44:20.556 in the chat has a question.
NOTE Confidence: 0.5595026383333333

00:44:20.560 --> 00:44:21.970 So we'll get him queued up
NOTE Confidence: 0.5595026383333333

00:44:21.970 --> 00:44:24.546 to ask it verbally.
NOTE Confidence: 0.5595026383333333

00:44:24.546 --> 00:44:26.248 Ian, very nice talk.
NOTE Confidence: 0.5595026383333333

00:44:26.248 --> 00:44:27.240 And this question actually
NOTE Confidence: 0.5595026383333333

00:44:27.240 --> 00:44:28.040 is a little bit similar
NOTE Confidence: 0.873849317142857

00:44:28.040 --> 00:44:29.440 to I think what Joe's getting at.
NOTE Confidence: 0.9309226166666667

00:44:30.880 --> 00:44:34.340 So you've shown that in the the subset
NOTE Confidence: 0.9309226166666667

00:44:34.340 --> 00:44:36.190 of the temozolomide treated patients
NOTE Confidence: 0.9309226166666667

00:44:36.190 --> 00:44:37.800 developed this hypermutated phenotype
NOTE Confidence: 0.9309226166666667

00:44:37.800 --> 00:44:39.666 and that's associated that leads to
NOTE Confidence: 0.9309226166666667

00:44:39.666 --> 00:44:42.760 poor outcomes in those patients.
NOTE Confidence: 0.9309226166666667

00:44:42.760 --> 00:44:44.258 It would seem that if you could
NOTE Confidence: 0.9309226166666667

00:44:44.258 --> 00:44:45.427 potentially if you could identify

NOTE Confidence: 0.930922616666667

00:44:45.427 --> 00:44:46.867 those patients up front who were

NOTE Confidence: 0.930922616666667

00:44:46.867 --> 00:44:48.655 going to go down that path with

NOTE Confidence: 0.930922616666667

00:44:48.655 --> 00:44:49.667 treatment with temozolemid that

NOTE Confidence: 0.930922616666667

00:44:49.667 --> 00:44:51.936 you may decide it may be in their

NOTE Confidence: 0.930922616666667

00:44:51.936 --> 00:44:53.983 overall better outcome to avoid using

NOTE Confidence: 0.930922616666667

00:44:53.983 --> 00:44:55.200 temozolemid in those patients.

NOTE Confidence: 0.930922616666667

00:44:55.200 --> 00:44:59.080 So if you looked at baseline molecular,

NOTE Confidence: 0.930922616666667

00:44:59.080 --> 00:45:01.080 molecular genomic characteristics

NOTE Confidence: 0.930922616666667

00:45:01.080 --> 00:45:03.360 of the patients who go on to develop

NOTE Confidence: 0.930922616666667

00:45:03.360 --> 00:45:04.810 hypermutator phenotype to be able to

NOTE Confidence: 0.930922616666667

00:45:04.810 --> 00:45:06.400 if you could predict those up front,

NOTE Confidence: 0.637769775714286

00:45:06.880 --> 00:45:08.091 yeah. So for ID, it's wild type

NOTE Confidence: 0.637769775714286

00:45:08.091 --> 00:45:09.440 of course we have a great marker.

NOTE Confidence: 0.637769775714286

00:45:09.440 --> 00:45:11.360 It's MGMT methylation, right.

NOTE Confidence: 0.637769775714286

00:45:11.360 --> 00:45:13.592 So for that, I would say that's

NOTE Confidence: 0.637769775714286

00:45:13.592 --> 00:45:14.760 already most largely addressed.
NOTE Confidence: 0.637769775714286

00:45:14.760 --> 00:45:15.882 For IDH mutants,
NOTE Confidence: 0.637769775714286

00:45:15.882 --> 00:45:19.279 we have not looked at this very much yet.
NOTE Confidence: 0.637769775714286

00:45:19.280 --> 00:45:20.840 There's been another publication from
NOTE Confidence: 0.637769775714286

00:45:20.840 --> 00:45:23.069 a group in China that has established
NOTE Confidence: 0.637769775714286

00:45:23.069 --> 00:45:26.320 a large number of serial cases.
NOTE Confidence: 0.637769775714286

00:45:26.320 --> 00:45:30.255 They have suggested that low level changes
NOTE Confidence: 0.637769775714286

00:45:30.255 --> 00:45:34.160 in chromosome 8 would be predictive of
NOTE Confidence: 0.637769775714286

00:45:34.160 --> 00:45:36.370 risk of developing hypermutation and
NOTE Confidence: 0.637769775714286

00:45:36.370 --> 00:45:38.920 they link that functionally to MIC.
NOTE Confidence: 0.637769775714286

00:45:38.920 --> 00:45:40.876 I think that data is interesting.
NOTE Confidence: 0.637769775714286

00:45:40.880 --> 00:45:43.365 I think it could use some further
NOTE Confidence: 0.637769775714286

00:45:43.365 --> 00:45:44.830 validation now as we are expanding
NOTE Confidence: 0.637769775714286

00:45:44.830 --> 00:45:46.320 and working on our glass effort,
NOTE Confidence: 0.637769775714286

00:45:46.320 --> 00:45:49.796 a major change relative to our latest
NOTE Confidence: 0.637769775714286

00:45:49.796 --> 00:45:51.844 release and one we are working on right

NOTE Confidence: 0.637769775714286
00:45:51.844 --> 00:45:53.587 now is that we've accumulated a large
NOTE Confidence: 0.637769775714286
00:45:53.587 --> 00:45:55.396 amount of whole genome sequencing data.
NOTE Confidence: 0.637769775714286
00:45:55.400 --> 00:45:56.798 And I'm excited about that because
NOTE Confidence: 0.637769775714286
00:45:56.798 --> 00:45:57.960 with whole genome sequencing data,
NOTE Confidence: 0.637769775714286
00:45:57.960 --> 00:46:00.054 you can do things with mutational
NOTE Confidence: 0.637769775714286
00:46:00.054 --> 00:46:01.450 signatures and mutational signatures
NOTE Confidence: 0.637769775714286
00:46:01.503 --> 00:46:02.799 would reflect for example,
NOTE Confidence: 0.637769775714286
00:46:02.800 --> 00:46:05.115 potentially DNA damage repair processes
NOTE Confidence: 0.637769775714286
00:46:05.115 --> 00:46:08.000 that are ongoing in these tumors.
NOTE Confidence: 0.637769775714286
00:46:08.000 --> 00:46:10.320 So I'm hopeful that we can identify tumors
NOTE Confidence: 0.637769775714286
00:46:10.320 --> 00:46:12.208 that have DNA damage repair processes
NOTE Confidence: 0.637769775714286
00:46:12.208 --> 00:46:14.925 going on and that that would then be
NOTE Confidence: 0.637769775714286
00:46:14.925 --> 00:46:16.880 repredictive of response to demasolomide.
NOTE Confidence: 0.637769775714286
00:46:16.880 --> 00:46:17.921 That's all speculation.
NOTE Confidence: 0.637769775714286
00:46:17.921 --> 00:46:20.799 So hopefully in a year from now or so,
NOTE Confidence: 0.637769775714286

00:46:20.800 --> 00:46:22.840 we will have more definitive answers.

NOTE Confidence: 0.637769775714286

00:46:22.840 --> 00:46:23.226 Thanks.

NOTE Confidence: 0.637769775714286

00:46:23.226 --> 00:46:23.612 Great.

NOTE Confidence: 0.637769775714286

00:46:23.612 --> 00:46:24.234 Doctor Contessa,

NOTE Confidence: 0.637769775714286

00:46:24.234 --> 00:46:25.638 I'm told we don't have access

NOTE Confidence: 0.637769775714286

00:46:25.640 --> 00:46:26.600 to allow him to talk.

NOTE Confidence: 0.864685385

00:46:27.080 --> 00:46:30.520 Can I can you hear me a miracle?

NOTE Confidence: 0.864685385

00:46:30.520 --> 00:46:32.472 Yeah, this is OK go ahead.

NOTE Confidence: 0.864685385

00:46:32.472 --> 00:46:35.472 Oh, great role. That was fantastic.

NOTE Confidence: 0.864685385

00:46:35.472 --> 00:46:38.640 Fantastic talk, very exciting.

NOTE Confidence: 0.864685385

00:46:38.640 --> 00:46:40.390 So yeah, I just wanted to drill

NOTE Confidence: 0.864685385

00:46:40.390 --> 00:46:42.231 down a little bit on the the

NOTE Confidence: 0.864685385

00:46:42.231 --> 00:46:44.115 radiation induced mutations because

NOTE Confidence: 0.864685385

00:46:44.115 --> 00:46:46.408 there is this question, right.

NOTE Confidence: 0.864685385

00:46:46.408 --> 00:46:48.856 Is it that you're select that

NOTE Confidence: 0.864685385

00:46:48.856 --> 00:46:51.011 after radiation it's a selective

NOTE Confidence: 0.864685385

00:46:51.011 --> 00:46:53.156 pressure and you're winding up

NOTE Confidence: 0.864685385

00:46:53.160 --> 00:46:55.920 you know finding those those

NOTE Confidence: 0.864685385

00:46:55.920 --> 00:46:58.867 mutations that have gone on and been

NOTE Confidence: 0.864685385

00:46:58.867 --> 00:47:01.560 propagated in in different clones.

NOTE Confidence: 0.864685385

00:47:01.560 --> 00:47:03.312 And you know I think that

NOTE Confidence: 0.864685385

00:47:03.312 --> 00:47:04.480 the main question is,

NOTE Confidence: 0.864685385

00:47:04.480 --> 00:47:07.238 so if you're sequencing from a tumor

NOTE Confidence: 0.864685385

00:47:07.240 --> 00:47:08.572 and considering the stochastic

NOTE Confidence: 0.864685385

00:47:08.572 --> 00:47:10.570 nature of radiation are do you

NOTE Confidence: 0.864685385

00:47:10.626 --> 00:47:12.649 think you're going to be able to

NOTE Confidence: 0.864685385

00:47:12.649 --> 00:47:14.840 find those recurrent you know,

NOTE Confidence: 0.864685385

00:47:14.840 --> 00:47:17.168 small deletions and isn't that

NOTE Confidence: 0.864685385

00:47:17.168 --> 00:47:18.848 probably more consistent with you

NOTE Confidence: 0.864685385

00:47:18.848 --> 00:47:20.962 have a resistant clone which might

NOTE Confidence: 0.864685385

00:47:20.962 --> 00:47:23.461 be you know have adna repair defect

NOTE Confidence: 0.864685385

00:47:23.461 --> 00:47:25.356 which enables radiation resistance and
NOTE Confidence: 0.864685385

00:47:25.356 --> 00:47:29.320 so then you wind up having that you
NOTE Confidence: 0.864685385

00:47:29.320 --> 00:47:31.720 know radiation resistant clone moving on.
NOTE Confidence: 0.864685385

00:47:31.720 --> 00:47:33.200 And I and I think that's similar to
NOTE Confidence: 0.864685385

00:47:33.200 --> 00:47:34.719 what you would see with CDK and 2A,
NOTE Confidence: 0.864685385

00:47:34.720 --> 00:47:35.638 but I won't be too long.
NOTE Confidence: 0.864685385

00:47:35.640 --> 00:47:37.397 And I guess my main question is,
NOTE Confidence: 0.864685385

00:47:37.400 --> 00:47:39.192 so can you know you have these
NOTE Confidence: 0.864685385

00:47:39.192 --> 00:47:39.960 two different possibilities,
NOTE Confidence: 0.864685385

00:47:39.960 --> 00:47:42.360 Could you use a single cell analysis to
NOTE Confidence: 0.864685385

00:47:42.360 --> 00:47:45.360 analysis to try to differentiate between,
NOTE Confidence: 0.864685385

00:47:45.360 --> 00:47:45.764 right.
NOTE Confidence: 0.864685385

00:47:45.764 --> 00:47:47.784 Is it the radiation that's
NOTE Confidence: 0.864685385

00:47:47.784 --> 00:47:49.800 the cause or just the,
NOTE Confidence: 0.864685385

00:47:49.800 --> 00:47:50.950 you know that it's the
NOTE Confidence: 0.864685385

00:47:50.950 --> 00:47:51.640 the selective pressure?

NOTE Confidence: 0.878832188888889

00:47:52.440 --> 00:47:52.936 Yeah. Thanks.

NOTE Confidence: 0.878832188888889

00:47:52.936 --> 00:47:54.672 Thanks very much and and great question.

NOTE Confidence: 0.878832188888889

00:47:54.680 --> 00:47:57.940 So if we take hybrid mutation

NOTE Confidence: 0.878832188888889

00:47:57.940 --> 00:47:59.640 following temozolomide as an example,

NOTE Confidence: 0.878832188888889

00:47:59.640 --> 00:48:02.305 because of the specific mutational

NOTE Confidence: 0.878832188888889

00:48:02.305 --> 00:48:04.437 signatures of mutations acquired

NOTE Confidence: 0.878832188888889

00:48:04.440 --> 00:48:05.892 after mint temozolomide,

NOTE Confidence: 0.878832188888889

00:48:05.892 --> 00:48:08.796 we're pretty sure that temozolomide is

NOTE Confidence: 0.878832188888889

00:48:08.796 --> 00:48:11.239 actually causing these these changes.

NOTE Confidence: 0.878832188888889

00:48:11.240 --> 00:48:13.529 And I think there's a lot of

NOTE Confidence: 0.878832188888889

00:48:13.529 --> 00:48:14.989 similarities between the small

NOTE Confidence: 0.878832188888889

00:48:14.989 --> 00:48:17.696 deletions acquired by after irradiation

NOTE Confidence: 0.878832188888889

00:48:17.696 --> 00:48:20.520 to the temozolomite example.

NOTE Confidence: 0.867935356111111

00:48:22.560 --> 00:48:24.471 One reason for saying that is that

NOTE Confidence: 0.867935356111111

00:48:24.471 --> 00:48:26.634 we have taken cell line models and

NOTE Confidence: 0.867935356111111

00:48:26.634 --> 00:48:28.784 irradiated them and then passes them for

NOTE Confidence: 0.867935356111111

00:48:28.784 --> 00:48:31.469 25 times or so or have made sure they

NOTE Confidence: 0.867935356111111

00:48:31.469 --> 00:48:34.216 went through a full cell cycle 25 * /

NOTE Confidence: 0.867935356111111

00:48:34.216 --> 00:48:37.240 a period of let's say 3 or so months.

NOTE Confidence: 0.867935356111111

00:48:37.240 --> 00:48:38.812 One of our MDP disease students

NOTE Confidence: 0.867935356111111

00:48:38.812 --> 00:48:40.360 has done that in the lab.

NOTE Confidence: 0.867935356111111

00:48:40.360 --> 00:48:41.944 And she said she showed that

NOTE Confidence: 0.867935356111111

00:48:41.944 --> 00:48:43.000 after about 3 months,

NOTE Confidence: 0.867935356111111

00:48:43.000 --> 00:48:45.086 you see a significant increase in the

NOTE Confidence: 0.867935356111111

00:48:45.086 --> 00:48:46.998 number of small deletions and tumors

NOTE Confidence: 0.867935356111111

00:48:46.998 --> 00:48:49.238 with or in cell lines with radiation

NOTE Confidence: 0.867935356111111

00:48:49.301 --> 00:48:51.716 versus those that have not been irradiated.

NOTE Confidence: 0.867935356111111

00:48:51.720 --> 00:48:52.420 And actually,

NOTE Confidence: 0.867935356111111

00:48:52.420 --> 00:48:54.870 and she actually spoke with your student

NOTE Confidence: 0.867935356111111

00:48:54.870 --> 00:48:57.436 after her exciting talk just two weeks ago.

NOTE Confidence: 0.867935356111111

00:48:57.440 --> 00:48:59.600 So that to me suggests a

NOTE Confidence: 0.867935356111111
00:48:59.600 --> 00:49:01.040 pretty strong causal link.
NOTE Confidence: 0.867935356111111
00:49:01.040 --> 00:49:03.758 Also, the types of small deletions,
NOTE Confidence: 0.867935356111111
00:49:03.760 --> 00:49:05.435 we've now made some progress
NOTE Confidence: 0.867935356111111
00:49:05.435 --> 00:49:06.440 in analyzing them.
NOTE Confidence: 0.867935356111111
00:49:06.440 --> 00:49:08.480 They carry a specific signature or they are
NOTE Confidence: 0.867935356111111
00:49:08.480 --> 00:49:10.078 associated with this specific signature,
NOTE Confidence: 0.867935356111111
00:49:10.080 --> 00:49:11.740 which again to me suggested
NOTE Confidence: 0.867935356111111
00:49:11.740 --> 00:49:13.793 there's a direct causal link rather
NOTE Confidence: 0.867935356111111
00:49:13.793 --> 00:49:15.725 than radiation causing clonal
NOTE Confidence: 0.867935356111111
00:49:15.725 --> 00:49:18.400 outgrowth of a particular clone.
NOTE Confidence: 0.895221368571429
00:49:21.480 --> 00:49:22.677 Yeah, I think that's what I wanted.
NOTE Confidence: 0.720555691666667
00:49:22.840 --> 00:49:24.705 Yeah, thanks. We should connect
NOTE Confidence: 0.720555691666667
00:49:24.705 --> 00:49:26.963 because I I have some some
NOTE Confidence: 0.720555691666667
00:49:26.963 --> 00:49:28.399 more comments and discussion.
NOTE Confidence: 0.49883337
00:49:29.080 --> 00:49:31.080 Great. I would love to. OK, I I just
NOTE Confidence: 0.799842923333333

00:49:31.080 --> 00:49:33.318 unmuted. Doctor Robinson, do you want
NOTE Confidence: 0.7829684725

00:49:33.320 --> 00:49:34.200 to ask your question?
NOTE Confidence: 0.67398930875

00:49:35.560 --> 00:49:36.415 Yeah, phenomenal talk.
NOTE Confidence: 0.67398930875

00:49:36.415 --> 00:49:37.840 I was going to ask,
NOTE Confidence: 0.67398930875

00:49:37.840 --> 00:49:39.166 I think you already answered this
NOTE Confidence: 0.67398930875

00:49:39.166 --> 00:49:40.479 about the MGMT methylate if there's
NOTE Confidence: 0.67398930875

00:49:40.480 --> 00:49:41.920 a difference in patterns resistance.
NOTE Confidence: 0.67398930875

00:49:41.920 --> 00:49:43.992 But the other question I was going
NOTE Confidence: 0.67398930875

00:49:43.992 --> 00:49:45.700 to ask is you know has there
NOTE Confidence: 0.67398930875

00:49:45.700 --> 00:49:46.930 been efforts to kind of pursue
NOTE Confidence: 0.67398930875

00:49:46.974 --> 00:49:48.194 synthetic lethal screens of some
NOTE Confidence: 0.67398930875

00:49:48.194 --> 00:49:49.559 of these identified pathways,
NOTE Confidence: 0.67398930875

00:49:49.560 --> 00:49:53.160 So CD and K things like that,
NOTE Confidence: 0.688124911666667

00:49:53.160 --> 00:49:56.238 That's a, it's a great suggestion.
NOTE Confidence: 0.688124911666667

00:49:56.240 --> 00:49:57.480 My speculation is that probably
NOTE Confidence: 0.688124911666667

00:49:57.480 --> 00:49:58.472 somebody has done that.

NOTE Confidence: 0.688124911666667
00:49:58.480 --> 00:50:00.955 We're not doing those in the lab right now.
NOTE Confidence: 0.688124911666667
00:50:00.960 --> 00:50:03.090 I guess you know challenges of
NOTE Confidence: 0.688124911666667
00:50:03.090 --> 00:50:05.600 course exist even though tell us this
NOTE Confidence: 0.688124911666667
00:50:05.600 --> 00:50:07.737 exists of course with getting any
NOTE Confidence: 0.688124911666667
00:50:07.737 --> 00:50:09.759 kind of molecules into the brain,
NOTE Confidence: 0.688124911666667
00:50:09.760 --> 00:50:11.720 you know if you have a target
NOTE Confidence: 0.688124911666667
00:50:11.720 --> 00:50:13.484 most many of our clinical trial
NOTE Confidence: 0.688124911666667
00:50:13.484 --> 00:50:15.288 failures that we've seen so far
NOTE Confidence: 0.688124911666667
00:50:15.288 --> 00:50:16.992 are actually related to blood brain
NOTE Confidence: 0.688124911666667
00:50:16.992 --> 00:50:18.719 barrier and and things like that.
NOTE Confidence: 0.688124911666667
00:50:18.720 --> 00:50:20.058 So I think your your your
NOTE Confidence: 0.688124911666667
00:50:20.058 --> 00:50:21.519 idea of course is very good.
NOTE Confidence: 0.891746136363636
00:50:24.040 --> 00:50:25.642 It'll take a little bit longer
NOTE Confidence: 0.891746136363636
00:50:25.642 --> 00:50:26.920 before we can actually see
NOTE Confidence: 0.75949041
00:50:29.320 --> 00:50:31.036 drugs and treatments materialize from that.
NOTE Confidence: 0.573872272

00:50:31.720 --> 00:50:32.960 And one follow up question,
NOTE Confidence: 0.573872272

00:50:32.960 --> 00:50:34.772 one thing that's always really been
NOTE Confidence: 0.573872272

00:50:34.772 --> 00:50:37.330 perplexing to me is that with EGFR 3 variants
NOTE Confidence: 0.573872272

00:50:37.330 --> 00:50:39.560 that if you put those in a Petri dish,
NOTE Confidence: 0.573872272

00:50:39.560 --> 00:50:40.840 those get selected out.
NOTE Confidence: 0.573872272

00:50:40.840 --> 00:50:42.120 So they're actually disadvantageous
NOTE Confidence: 0.573872272

00:50:42.120 --> 00:50:43.360 in a Petri dish.
NOTE Confidence: 0.573872272

00:50:43.360 --> 00:50:44.824 But obviously we see them in
NOTE Confidence: 0.573872272

00:50:44.824 --> 00:50:45.800 in real human tumors.
NOTE Confidence: 0.573872272

00:50:45.800 --> 00:50:47.536 Do you have any any kind of
NOTE Confidence: 0.573872272

00:50:47.536 --> 00:50:49.242 sense or any insights as to
NOTE Confidence: 0.573872272

00:50:49.242 --> 00:50:51.128 why those are advantageous in
NOTE Confidence: 0.573872272

00:50:51.128 --> 00:50:51.960 the real human environment,
NOTE Confidence: 0.573872272

00:50:51.960 --> 00:50:53.115 But they're not in a Petri dish,
NOTE Confidence: 0.822031721428571

00:50:54.240 --> 00:50:57.516 so it's hard to answer that directly.
NOTE Confidence: 0.822031721428571

00:50:57.520 --> 00:51:01.331 Maybe it has to do with the types of

NOTE Confidence: 0.822031721428571

00:51:01.331 --> 00:51:03.690 ligands that exist in the micro environment

NOTE Confidence: 0.822031721428571

00:51:03.752 --> 00:51:06.160 versus those that exist in a Petri dish.

NOTE Confidence: 0.822031721428571

00:51:06.160 --> 00:51:08.408 The the spin I would gift on this

NOTE Confidence: 0.822031721428571

00:51:08.408 --> 00:51:11.296 is that we find that all V3 variants

NOTE Confidence: 0.822031721428571

00:51:11.296 --> 00:51:13.516 exist on extra chromosomal DNAs.

NOTE Confidence: 0.822031721428571

00:51:13.520 --> 00:51:18.128 So EGFR is is amplified when the V3 is

NOTE Confidence: 0.822031721428571

00:51:18.128 --> 00:51:20.416 present and these amplifications typically

NOTE Confidence: 0.822031721428571

00:51:20.416 --> 00:51:22.636 reside on extra chromosomal DNAs.

NOTE Confidence: 0.822031721428571

00:51:22.640 --> 00:51:27.090 And there's a lot of, you know,

NOTE Confidence: 0.822031721428571

00:51:27.090 --> 00:51:30.600 that does a lot of things to these cells,

NOTE Confidence: 0.822031721428571

00:51:30.600 --> 00:51:32.760 including potentially putting a higher

NOTE Confidence: 0.822031721428571

00:51:32.760 --> 00:51:35.702 burden on the cells to produce all

NOTE Confidence: 0.822031721428571

00:51:35.702 --> 00:51:37.951 the DNA needed for the high numbers

NOTE Confidence: 0.822031721428571

00:51:37.951 --> 00:51:39.613 of copies that typically exist when

NOTE Confidence: 0.822031721428571

00:51:39.613 --> 00:51:40.959 there's extra chromosomal DNA.

NOTE Confidence: 0.822031721428571

00:51:40.960 --> 00:51:43.078 So that could be one reason.

NOTE Confidence: 0.822031721428571

00:51:43.080 --> 00:51:44.064 And in general,

NOTE Confidence: 0.822031721428571

00:51:44.064 --> 00:51:47.930 I think EC DNA is very potent in

NOTE Confidence: 0.822031721428571

00:51:47.930 --> 00:51:49.912 many ways and that probably has

NOTE Confidence: 0.822031721428571

00:51:49.912 --> 00:51:51.582 to do with why these are selected

NOTE Confidence: 0.822031721428571

00:51:51.582 --> 00:51:53.318 out more so than the V3 itself.