Making_It_Personal__Using_DNA_to_Tailor_Cancer_Treatments__English__mp4_

[00:00:00.00]

[00:00:20.31] PROFESSOR LIAO: Welcome to our segment on how to choose the best cancer therapy to treat individual tumors. I'm Rachel, and I work in the cancer program at the Broad Institute of Harvard and MIT in Cambridge, Massachusetts. Today we're going to talk about lung cancer, which is a disease that can affect people who are both smokers and non-smokers.

[00:00:39.30] Our whole lesson today is going to focus on three patients whose details I have here. Patient number one is a female Asian non-smoker, who's 46 years old. Patient number two is a female Caucasian non-smoker, who's 54 years old. And patient number three is a male Caucasian former smoker, who's 75 years old, who smoked one pack of cigarettes per day for 20 years until he quit when he was 55.

[00:01:07.00] All of these patients have recently been diagnosed with stage III lung cancer, but that doesn't mean that all of their tumors are exactly the same. Here are three pictures of each of their individual tumor cells, which have been stained so that you can see the nucleus in bluish purple and the outline of the cells, which is reddish pink. And I want you to determine what the similarities and differences are between each of the images, and also what you want to know next in order to treat each individual patient. I'll give you a couple of minutes to do that with your class.

[00:01:47.47] Welcome back. Based on the images you just saw, it can be hard for doctors to determine the best treatment for a patient, because tumors that look the same may respond to different types of therapies. But at the end of this lesson, you are going to make a recommendation for each patient of which sort of treatment they should receive.

[00:02:05.68] There are three common types of cancer treatment. The first is surgery. If a tumor is small enough, that can be cut right out of a patient. The second is radiation, where a tumor is exposed to high levels of energy. And the third is with anti-cancer drugs.

[00:02:20.45] There are two categories of anti-cancer drugs. One is called targeted therapy, and the other is called chemotherapy. In the first half of this image, you can see a targeted therapy agent, which is a small molecule binding to a mutant form of a protein that's only found in cancer.

[00:02:36.17] In the second half of the image, you can see a chemotherapy, which is binding to DNA polymerase, which is the enzyme that replicates DNA. This enzyme is active in cancer cells, but it's also active in any dividing cell, like bone marrow or skin or intestinal lining.

[00:02:52.24] Your assignment is to decide which of these two therapies, targeted therapy or chemotherapy, is going to have the most side effects and why. I'll give you a couple of minutes to talk that over with your class.

[00:03:13.61] Welcome back. Hopefully, you realize from your discussion that chemotherapy would have the most side effects of any of the therapies, because chemotherapy doesn't just target cancer cells. It target any dividing cell. That can include bone marrow or skin or the intestinal lining. And that's why many patients who get chemotherapy have secondary infections, they lose their hair, and they also get very nauseous.

[00:03:35.72] Now I'm going to present to you an analogy of chemotherapy and targeted therapy where the kitchen is the cell and the appliances that I have here are each a protein in the cell. Usually, you can turn them on and off. And that's very useful. But say that you couldn't turn them off.

[00:03:53.58] If I wanted to make a coffee smoothie and I needed a coffee maker and a blender, in one kitchen my coffee maker is out of control and keeps dripping coffee into my cup even after it's full. Or in another kitchen, my blender is out of control and spews all of its liquid out of the top and doesn't stay inside. The problem is that they're both out of control.

[00:04:15.14] Now I want you to do an assignment where you determine the best way to fix each individual broken appliance. You can either use a rubber stopper or you can use a lid or you can turn off the power to the whole kitchen. I'll give you a couple of minutes to talk it over with your class, and I'll see you soon.

[00:04:41.46] Welcome back. Hopefully, in your last activities you saw that the stopper was the best way to fix a broken coffee maker, the lid was the best way to fix a broken blender, and turning off the power would fix both the broken appliances, but it would also lead to the side effect of not being able to use your kitchen anymore.

[00:04:58.35] That was our analogy, right? That the kitchen was like a cell, and the appliances were like the proteins in the cells. Now, just like you have instructions to make a blender, and if there are mistakes in those instructions then you'll have a faulty product. The DNA is the instructions to make proteins. And if you have mistakes in your DNA, then it'll also make a faulty protein.

[00:05:19.39] Now sometimes we can visualize the mistakes in DNA by looking at it under a microscope. My colleague Melanie is going to show you how we do that.

[00:05:30.57] PROFESSOR DONAHUE: Hi. My name is Melanie. And like Rachel, I work in the cancer program at the Broad Institute. I'm going to show you now some images of DNA from each of the patients that we'll be talking about.

[00:05:40.92] Before I do that, I'd like to explain a little bit about where we get these images from. We can use a fluorescent microscope, like the one you see here, and a computer program, like this, to take images of DNA in cells that have been fluorescently labeled.

[00:05:54.17] But before I show you those photos, I'd also like to explain what this DNA comes from and what it looks like. Each chromosome has two versions in your DNA, one maternal and one paternal, meaning one from your mother and one from your father. Each of these versions also includes two replicates strung together. These replicates are identical copies of each other produced when your DNA replicates during normal cell division.

[00:06:16.83] We're now going to show you some photos of DNA from all of our patients. In these photos we're going to ask that you look for rearrangements in the DNA. We've labeled the few genes, one Gene A in red, and one Gene B in green. A rearrangement of these genes, where these genes come very close together on a chromosome, will look yellow, meaning that the colors are right on top of each other.

[00:06:38.38] Now we ask that you look at these pictures and tell us if you see any rearrangements, and in which patients these arrangements are. Take a moment to discuss it amongst yourselves and with your teacher. And we'll see you soon.

[00:06:58.70] PROFESSOR LIAO: Welcome back. In our last exercise, you saw that patient number two is the patient with the genetic rearrangement. But not all cancers are caused by genomic events that are as large as a whole rearrangement. Some are much smaller, and a genetic mutation is caused by an individual base changing at the genetic level.

[00:07:19.14] Here's a diagram of the difference in size between a big rearrangement and a single base that's being mutated. Historically, scientists have had to run big experiments manually, like this one, where they count each individual base as it's sequenced. But now, we can use big robots, like this one behind me, which colors each individual base, the A's, T's, C's, and G's, a different color. And then scientists can read out the colors in order and tell what this sequence of the DNA is.

[00:07:48.30] The DNA sequence is detected right here. The four colors, blue, red, green, and yellow, can be ordered by scientists so that the DNA sequence can be determined. This is an older version of the machine, but now we're going to take you into a lab where newer sequencers are actually running and reading people's DNA sequence right now.

[00:08:07.32] Now I'm going to show you one of those chromatograms, the ordering of the different colors that corresponds to the DNA of the patient, right here. Each color represents one base from the patient's DNA. Your assignment is going to be to look at two genes that are commonly mutated in lung cancer patients, EGFR and

KRAS, and to evaluate the chromatograms from each patient's DNA for each of those genes. I'm going to give you a couple of minutes now to talk to your classmates and your teachers and determine which genes have mutations in which patients.

[00:08:49.43] Welcome back. By now, we've seen photos of whole cells, photos of DNA, and DNA sequence for each of our patients. Now, I want you to summarize everything we know about each patient in terms of EGFR mutation and KRAS mutation and rearrangement in the chart in your handout. And then I want you to make recommendations for treatment based on the table of response rates that's on your handout.

[00:09:15.45] Now in the response rates chart, each percentage refers to the number of patients who had a positive response on that anti-cancer drug. I'll give you a couple of minutes to work on that with your class.

[00:09:36.75] Welcome back. You've probably seen by now that patient one has an EGFR mutation, patient two has a rearrangement, and patient three has a KRAS mutation, which means that patient one should be treated with erlotinib, which is a targeted therapy, patient two should receive crizotinib, which is also a targeted therapy, and patient three should receive regular chemotherapy.

[00:09:59.40] This demonstrates how there are many different cures for many different tumors based on what genomic event each tumor possesses. And that's something that's very different from the way that tumors were treated 10 years ago, before tumors were sequenced routinely to look at which genomic event might be there. 10 years ago, every tumor would have received the same treatment, even though many patients would not have responded as well as they respond to different targeted therapies.

[00:10:25.75] This pie chart shows you the number of lung cancer patients who have rearrangements, and EGFR mutations, and KRAS mutations. But it also shows you that many lung cancer patients' tumors have no known events in their genomes that drive their cancer, and therefore no treatment that we can give them that will target their tumor.

[00:10:46.75] One major focus in the Broad Institute's cancer program is to determine what falls into this category currently called unknown for different lungs cancers and to determine effective therapies that can be used to treat these patients. I hope you've been able to see that there are many benefits to DNA sequencing, but there are also many ethical concerns. And if you're interested in questions relating to those concerns, I encourage you to check out our extension activity on bioethics.

[00:11:15.33] I hope you've enjoyed our lesson on how to choose the best therapy for individual tumors. Thanks for joining us.

[00:11:32.02] PROFESSOR ROKOP: Hi. Thank you for considering using our lesson from the Broad Institute cancer program on choosing the right treatments for

different kinds of tumors. The learning objectives for these lessons are to evaluate a series of pieces of data from tumors from three patients. There will be pictures of the cells, pictures of chromosomes within the cells, and also DNA sequences from two different genes in those cells. The objective will be that the students will evaluate these data to determine which of a series of treatments would be the best treatment for each different kind of cancer.

[00:12:06.19] The prerequisite knowledge is minimal. It is helpful if the students know that DNA's the genetic material and that mutations are changes in the DNA, and that there can be both single nucleotide changes and also a large scale changes, such as translocations and inversions. It's also helpful if the students know that DNA is transcribed into RNA and translated into protein.

[00:12:28.39] The only really necessary supplies are the handouts and the slides provided with the lesson.

[00:12:33.98] The lesson is a series of seven segments. In the first segment, the three patients are introduced to the students as characteristics in terms of whether they're male or female, and their age, and whether they're smokers or non-smokers. At the first segment, the activity is that the students receive images of cells from the tumors of these three patients. And they are asked to determine similarities and differences between those pictures of cells. They're also asked what would they want to know next about those patients in order to make a recommendation for a treatment.

[00:13:11.73] When we come back, we go through the major types of cancer treatments, radiation, surgery, and drug treatments. We go through the two different kinds of drug treatments, both chemotherapy and targeted treatments. We then have the students predict which type of drug treatment, either targeted treatments or chemotherapy, would have more side effects.

[00:13:33.59] When we come back in segment three, we given analogy for different proteins functioning in the cell as different appliances functioning in a kitchen. And when there are mutation, such that the appliances are overactive, there's different kinds of treatments that you would recommend based on which appliance has gone out of control.

[00:13:52.86] So the students are given different situations where there's an overactive blender and an overactive coffee machine. And their options for treatment are a lid or a rubber stopper or just turning the power off in the kitchen. The students then have an activity where they recommend the correct treatment for each of the different issues in the kitchen. And this is an analogy for chemotherapy versus targeted therapies used for different kinds of cancer.

[00:14:19.44] When we come back in segment four, we talk about how since the DNA are instructions for proteins, if there are changes in the DNA then faulty

proteins can be produced. And we can actually see whether there are changes in the DNA by looking at the chromosomes of the cells under fluorescence microscopes.

[00:14:35.92] The students see an example of such a microscope, and then they're given images of the chromosomes in tumors from the three patients. In these images, one gene is labeled red and another green. And if the rearrangement occurs, those two genes are brought very close together so that, instead, you see the red and the green combine to make a yellow dot. Thus the students are asked to analyze these images to determine whether there has been a rearrangement in the chromosomes or not.

[00:15:02.31] When we come back in segment five, we reveal that patient two had a rearrangement, whereas patients one and three didn't. So we then discuss how there are other changes in the DNA that are not large rearrangements, but rather changes in single letters or bases in the DNA. And we talk about how these changes can be detected using DNA sequencing.

[00:15:22.71] We then provide the students with DNA sequence data from two genes, EGFR and KRAS, that are often mutated in lung cancer. We provide the sequencing data in chromatograms of those two genes in each of the three patients. And then the students are asked to analyze those data and determine which genes have single letter differences in each of the three patients.

[00:15:46.15] When we come back in segment six, we give the students an assignment to compile all of the data that they've seen so far for the three patients, that is, the photographs of the cells, the photographs of the chromosomes, and also the DNA sequence data of the KRAS and EGFR genes.

[00:16:02.51] At this point, the students have to determine using all these pieces of data which mutation or genetic change has occurred in the tumors of these three patients. The students are then given response rates of how well patients respond to different kinds of drug treatments. Two of the drug treatments shown are targeted treatments, and one is a chemotherapy agent.

[00:16:23.54] The students are then asked to make recommendations of which treatment should be used with which patient, based on the genetic changes that have occurred in their cells and the response rates in the chart.

[00:16:35.08] Finally we come back in segment seven, we reveal which treatment is the best fit for each of the patients, based on the genetic makeup of their tumors. And we talk about how this lesson has demonstrated the principle that instead of there being one cure for cancer, there are many different kinds of treatments, each of which may be best for a different kind of tumor. We then talk about how DNA sequencing technology allows us to sequence the DNA in the tumors of these patients so that we can then determine which treatment may be best for them.

[00:17:05.91] Although there are benefits to being able to DNA sequence the DNA from these tumors, there are also ethical considerations to having DNA sequence of different people. And so we then offer the students the option of doing an extension activity on the bioethical considerations of having the information in your genome.

[00:17:27.03] And that's the end of our lesson. We hope you enjoy using it. And thank you for joining us.