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IT.edu. Cancer is a disease that really needs no introduction.

It's a very familiar disease. It's a very common disease.

The American Cancer Society predicts that there will be 1. million new cases of cancer in this country, and that excludes the common forms of skin cancer, squamous cell cancer, and basal cell cancer.

There's about another million of those. So, 1.

non-cutaneous skin cancers in the US this year. Both wide numbers are probably 10 to 15 times as many. In 2006, more than 550,000 people in the US -- More than 550, 00 people in the US will die from this disease --= -- more than 1, 00 each day. So, in today's, cancer takes as many lives as died in the World Trade Center tragedy. It's a very common disease.

It's estimated that in their lifetimes, one half of all males -- -- and a third of females will be diagnosed with cancer of one sort or another. So the likelihood is that the person sitting next to you, or you yourself will be faced with a diagnosis of cancer in your lifetime.

And in this country, a quarter of all deaths are due to cancer. Soon, probably this year, cancer will be the leading cause of death in the United States. It will surpass heart disease as the number one killer. So, it's a major disease.

And that sounds depressing. But by the end of this section on cancer, my hope is that you will actually feel optimistic about our prospects for dealing with the disease more effectively in the future, and I don't mean in the distant future.

I actually think that within the next several years, we'll have new methods, new agents to control cancer much, much more effectively. We are already starting to see the first examples of these. And I'll tell you about them.

And before long, we will have many more.

So hopefully by the time you guys are at the age where cancer is the greatest risk, these numbers will actually change dramatically. OK, so although cancer is familiar based on its prevalence, it may not be so familiar.

And I hope that is not so familiar in detail. So, I thought I would show you a couple of slides which really give you a picture of the disease. Lung cancer is a common type of cancer. We'll talk about it today. And it's diagnosed like many cancers are diagnosed through radiological methods, through imaging, in this case a chest x-ray or

computed tomography, which is a serial chest x-ray basically. And you can see this mass in the lung. This is lung cancer at a fairly advanced stage. Cancer is a disease of too many cells. They often grow together in a mass, a lump, and so this is an example of cancer diagnosis, a solid tumor.

You can also have cancers of the blood, leukemias, as well as blood cell lymphomas. And here, you can, again, see an overabundance of cells. Here's a normal blood smear with red blood cells, these smaller guys which have no nuclei, and some white blood cells which are larger and do have nuclei.

And here, you can see a blood smear of a leukemia patient where there are way too many white blood cells, nucleated cells, and they also happen to look a little immature. They have been differentiated into their fully developed state. Too many cells, in this case, not in a lump but dispersed throughout the blood.

And leukemias, and some lymphomas, are diagnosed by doing a blood test of this sort. Other cancers are detected through other imaging techniques like colonoscopy as shown here.

Colonoscopies are now fairly common. They are recommended for all people beyond the age of 50 because colon tumors are actually rather common.

And if they are caught early enough, there relatively easily treated.

And here's the normal colon viewed from the inside.

And here's an early colon tumor called a polyp.

And I'll give you a little more nomenclature in a minute.

But this is an early stage tumor, probably not a malignant tumor.

If you saw this tumor, you might not actually remove it because it might not progress to a full-scale cancer.

But these days, because they're pretty easy to remove using very similar methods as this gentleman here with the colonoscopy, one would clip them out, and not risk the possibility that they could progress. If they do progress, they get larger. And more importantly, they begin to invade through the wall of the colon. And this is very dangerous because now the cancer cells can spread throughout the body, taking up residence elsewhere and causing even greater problems for the patient. So, this would require surgery.

A section of the colon would be removed as is shown here.

This is a section of colon where the colon cancer is highlighted by this circle. And this is a life sparing surgery.

Individuals can live just fine. So if colon cancer is caught even at this stage, an advanced stage, but before it has spread to other parts of the body, it's relatively treatable, even curable by surgical methods.

Now, this set of pictures gives you a sense that cancers progress.

They progress from early-stage, relatively normal looking tissue through much more advanced cancers, including to the point of metastasis.

And we are beginning to understand this process in some detail both in terms of what the cells look like, the tissues look like, but also what the genes look like that are driving these processes forward.

And I'm now going to give you some examples, or introduce the concept, that cancer progression from normalcy to malignancy is associated with changes in genes. That's really going to be a major theme of today and in the following lectures. But histologically, the process looks like this in cartoon form.

One starts with a normal looking tissue. All of your cells are organized in one way or another in tissues, where they have important interactions with their neighboring cells: so here, a series of, say, epithelial cells.

Maybe these are the cells that line your gut. They are in normal juxtaposition with their neighbors. They are sitting atop what's called a basement membrane, proteins that are secreted by those cells and other cells to give the cell something literally to sit on it, attach to. And then there are other cells in their vicinity including the cells that give rise to these cells, the stem cells or precursor cells, of the tissue that will be called on to differentiate into these end stage cells when these cells are lost, sloughed off. At some frequency in all of us, alterations occur in these cells such that an abnormal cell arises.

This is a cell which has acquired a change. I'll tell you now that it's a genetic change which allows that cell to do things that its neighbors can't do. And in particular, it allows those cells to grow, to divide inappropriately. Your tissues are very carefully orchestrated systems with the appropriate numbers of cells.

And cancer is fundamentally a disease of too many cells.

And so one of the first things to go wrong in the cancer development process is this orderly cell division is disrupted such that now, too many cells are produced. And this results in a phenomena known as hyperplasia, hyperplasia meaning too many cells.

But importantly these cells look pretty normal.

So to the pathologist, and I'll show you some pathology slides in a second, to the pathologist, they would say the abnormal cells in number have a normal morphology.

Their shape looks right. Their internal structures look right. Their nuclei look right. This process can continue, and probably often does continue until there is a discernible mass at least when it comes to solid tumors, a discernible mass.

And here we refer to this as an adenoma. And I'll show you these terms again in a minute on the board, in this case, an adenoma, a benign tumor. And you heard that were before, benign, as opposed to malignant. And a benign tumor is a tumor in the sense that there are too many cells. So it's a mass.

But the cells look pretty normal. In a benign tumor, it's not considered to be life-threatening. The cells have not undergone sufficient changes that we know for sure that they're going to, for example, invade and spread throughout the body.

And oftentimes, benign tumors are left alone because they don't have the potential to spread or to become more aggressive.

But some of them do. And through additional changes within the cells, additional alterations take place such that now the cells really do look different from the neighbors. Their structures look different.

Their overall shape looks different. Their nuclei look different. Their interactions with the neighboring cells look different.

And the structure of the tissue changes as well in the sense that now, new blood vessels have been recruited into this mass, which was important actually in feeding this growing tumor.

This is true cancer. It's called in C2 cancer because it's present at the original site where the process started in C2 cancer.

And it's called cancer based on these various characteristics: how much the cells are growing, dividing, and also what the cells look like, their shape and their nuclear shape.

That's a problem. But it's a bigger problem because it facilitates and usually leads to the development of these tumors into an invasive state. So now, the cells are no longer staying where they started. They are starting to move out into the surrounding tissue. They break down, degrade the extracellular matrix, and actually start to migrate away from the primary tumor into the surrounding tissue, into the surrounding musculature, and ultimately into the blood vessels. It can move into the blood vessels.

And once there, they can move throughout the body, and escape the blood vessels, and take up residence elsewhere in a process known as metastasis. This process happens at some frequency once started. If it reaches

this point, it's a very bad situation. Most cancers that kill people, kill people because of this process of metastasis.

90% of cancer deaths are attributable to metastasis.

And although we know many of the things that happened over the course of these earlier stages, we actually know this process relatively less well. And obviously, we need to understand it better if we are going to control mortalities due to cancer. This shows you some histology.

These are slices through tumors and other tissue that a pathologist would look at, and kind of emphasizes the points that I was making on an earlier slide in cartoon form.

So, here you have a lung. And in it is some abnormal cells in the red circle here. There are too many cells compared to the surrounding tissue. You can see them in this kind of dark blue depiction. And you'll see it easier on your computer screens later. But again, these cells look relatively normal. There are just too many of them.

So we call this hyperplasia. These can progress into small and benign tumors called, in this case, adenomas.

And you can see on the histology that they are rather homogeneous in their structure. The cytoplasm looks pretty much the same. Cell to cell, the nuclei look pretty much the same cell to cell. And they actually look pretty similar to the normal cells that surround them. So this is not true cancer.

This is a benign tumor. But it can progress to a true cancer, adenocarcinomas. And you can see from the high magnification view that this looks very different from this.

The cells don't look the same one to the other, and their nuclei don't look the same either. And what you can't appreciate is that these cells are also dividing at a much greater rate compared to these cells. And so, this is true cancer. And this has the potential, then, to spread to metastatic disease. OK, so I've given you, there, all bunch of terminology. Let me tell you a bit more about it.

Hyperplasia: too many cells.

That's all it means. Hyper: too many. Plasia: growth, too much growth.

Hyperplasias can result in benign tumors, which are non-aggressive -- -- nondestructive -- And they, at this moment at least, have not spread to nearby tissue, non-aggressive meaning that the cells look pretty normal. They don't look different from their normal neighbors.

These can give rise to malignant tumors. And the word cancer is actually reserved for malignant tumors. If you have a tumor that's benign, you don't have cancer. Cancer refers to malignant tumors.

And these are different in the sense that they are aggressive.

The cells are much more active. They've changed their shape.

They've changed their structures.

They are destructive, that is, they secrete factors into the environment, which break down, for example, extracellular matrix.

And they have the potential to spread. They've begun to invade into the local environment, and can't access the blood supply.

OK, there are cancers in many of your organs in many different cell types within those organs. In the cancers in different places in your body are referred to by different terms.

For epithelial tissues, skin, intestines, breast, brain, lung, epithelial tissues, we call the tumors carcinomas.

Carcinomas, and depending on the particular cells that are affected, whether they are glandular cells or secretory cells, we can give them additional names, for example, an adenocarcinoma.

And that's a cancer that looks like the glands that give rise to the tumor in adenocarcinoma. And there could be adenocarcinomas in the different places that I mentioned previously.

And there are benign versions of this tumors. And for adenocarcinomas, the benign version the adenoma.

You can get tumors of connective tissues, and these are referred to as sarcomas. And there could be different sarcomas depending on where they are found, for example, various types of myosarcomas would be found in what type of tissue? These are muscle tumors, rhabdomyosarcomas, leiomyosarcomas. Another example are chondrosarcomas -- -- which are tumors of cartilage. In this class of tumors, which are called soft tissue tumors, were in the news just today as a matter of fact, front page of the Boston Globe if you happen to see it. There is a site, a former dye factory that was dumping pollutants into ponds and Ashland.

And they've just determined that the exposure to those dyes greatly increased the risk of children to later develop soft tissue sarcomas.

Several children then turning into 20, 30 year olds developed tumors of this type which fits to the theme of the lecture in terms of exposures leading to cancers.

Tumors of the blood system are referred to by different names, leukemias -- -- in which the tumor cells are in the

blood, B cell leukemias, T cell leukemias, erythroleukemias, myeloid leukemias where the cells are in the bloodstream like the one I showed you before, and lymphomas where the tumors are in the lymph organs like the spleen or the thymus or the lymph nodes. So, that gives you some terminology.

And I'll be referring to some of this terminology as we go through the remaining lectures. And it's just useful to know as you learn about and hear about cancers.

Now, cancer research, over the last several decades has been dedicated to try to understand this process of normalcy to malignancy. How does that happen? And the conclusion from all of this work, which I will review for you is that cancer is a genetic disease.

What do I mean by that? What do I mean by cancer is a genetic disease?

Does anybody want to hazard a guess? What do we normally think of when we talk about genetic diseases? Heritable diseases, predispositions to disease, we talked about several of them previously in the class like cystic fibrosis and many others. Cancer can be a genetic disease in that sense. There can be inherited predispositions to certain cancers.

And I'll mention some in later lectures. But in fact, all cancers are genetic diseases. All cancers arise through alterations in your genes. Those alterations in most cases are not inherited from one of your parents but are acquired through your lifetimes through mistakes or exposures to things that cause such changes. Why do we believe this so strongly?

Well, firstly, and this has been known for some time, cancer cells don't look normal chromosomally.

If you look at the chromosomes of normal cells, they're all the same.

All have 46 chromosomes. The chromosomes have proper structures but when you look at cancer cells, that's not true.

For most cancers, in contrast to the normal karyotype, the normal chromosomal number in architecture, and this is an image which highlights the different chromosomes by different colors.

This technique allows us to distinguish one chromosome from the other based on the color that it stains with these dyes that are used here. Anyway, this is a normal cell, 46 chromosomes. And here's a cancer cell. And it's different in many ways. There are way too many chromosomes.

So it's a defect in chromosome number. But it's also a defect in chromosome structure. And you can see in the boxes a couple of alterations here. There is a chromosome 7, which is lacking a little bit of its end. So it's got a

truncation. I think that's a seven. Actually, maybe that's not.

Many that's chromosome 24. Anyway, it doesn't matter. And here, you can see, it looks like an ice cream cone: a little bit of paint on the bottom, a little bit of green on the top.

This is a new kind of chromosome that has been fused by two different chromosomes coming together. So this is a translocation. And here's another translocation here. So, chromosomes and cancer cells are often abnormal in their structure. They can have translocations. They can have deletions.

They can have other kinds of rearrangements.

And so, based on this, we know that cancer has defects in its genomes, and ultimately we know in its genes.

We also know that agents that cause cancer -- -- and we refer to these as carcinogens -- -- cancer-causing agents, carcinogens are most often mutagens -- -- agents that cause mutations.

Carcinogens are mostly mutagens. And therefore, it's likely that the reason they are carcinogens is because they lead to mutations in cellular genes. We believe that very strongly, and it's based on work from many groups over long periods of time that have established this kind of correlation. To sort of prove the point, many, many agents, many, many things that have been suspected to be cancer-causing have been tested to see whether they are mutation causing, to see whether carcinogens are mutagens. And they are tested using assays -- -- like carcinogenicity assays where the compound in question or the agent, might be a physical agent like radiation, is tested to see whether it will promote tumor formation. And this is typically done in laboratory animals. So, you expose, say, a mouse or a rat to the agents in question, and you ask the question, over time, does that promote the formation of a discernible tumor?

If yes, then the agent is a carcinogen. OK, and then you ask the question, is the agent a mutagen -- -- using mutagenicity assays.

And these are typically done in bacteria because they can be done very, very rapidly. We can ask whether the agent is able to cause mutations in bacterial cells. And the standard assay that has been developed, and is still in use, is to take this agent, drop it into a broth carrying bacteria, and not just any bacteria, but bacteria that have mutation in a gene required for histidine synthesis.

They can't make their own histidine, the amino acid histidine. And so, for them to grow, they require histidine in the medium here, or in the medium on the plate, the agar plate that you grow them. If you were to take some of these histidine minus bacteria, and plate them on a tissue culture plate, or rather a bacterial plate, that lacked histidine would any of them grow? No, because they can make their own.



You have been given them any. So they can't grow into colonies.

You would get zero colonies if you did that. This is due to a mutation in a single gene. If you can create another mutation at that site and revert the abnormal gene into a normal gene, now the cells can make their own histidine. So, if you can mutate these cells back to becoming competent to make histidine, then if you plate these cells on a histidine minus plate, you might get colonies. You would get some colonies.

For every bacterial cell that acquired a mutation at the right site, fixing the histidine synthesis gene, now that cell would be able to grow into a colony. And actually, the potency of the mutagen determines how many colonies you get. So, you can have weakly acting mutagens or strongly acting mutagens. And as I mentioned, most agents that pass this test will also pass this test, OK?

However -- -- some known carcinogens fail that test. They clearly are carcinogens.

You paint them on the back of a mouse or feed it to an animal: the animal will develop cancer. And yet, when you do the bacterial reversion test, they don't show up as being mutagens.

Why is that so? Anybody? Yes?

They could be so mutagenic that they block the development of the bacteria at all. That's actually a very interesting idea, not what I was thinking of. But it's a good idea. They are super mutagens. So they fail the test for that reason. Anything else? What's different between this test of this mutagenicity, and what actually happens in the body? Anybody? Yes? That's good.

And I'll actually come back to that. There is another good suggestion, but I'll come back to that answer in a second.

The difference is metabolism. Your body metabolizes things that you get exposed to that you eat, or that you inhale, or that you inject yourselves with. It metabolizes it oftentimes to detoxify it or to make it more water-soluble so that you can excrete it. There is a lot of metabolism breaking down or changing the things that you get exposed to. And so, it's been observed that there are certain compounds which are not themselves mutagens but are pro-mutagens. They have the capacity to turn into mutagens.

And in the process of metabolic enzymes, they become mutagens.

And there are very important carcinogens that fall into this category. And one of them is shown here. This is a polycyclic hydrocarbon called benzoate pyrene. It's a very important ingredient in cigarette smoke as well as in barbecued beef.

It's a very potent carcinogen. It passes this test with flying colors. But if you do the bacterial reversion test, you don't see anything. And the reason is that in the body, many of these double bonds had to be broken and replaced ultimately by hydroxyl groups to make this compound more water-soluble so that it can be excreted. And an intermediate step in the detoxification, the hydroxylation, is the formation of epoxide. And these epoxides are actually highly reactive to DNA. And these molecules, these intermediates, are highly mutagenic.

And so, when you make these in your body, thinking you're doing a good thing, you're actually doing a bad thing by creating a mutagen.

And it's this that's the mutagenic agent. And so, now the simple bacterial reversion test has been replaced by something called the Ames test named after Bruce Ames from Berkeley in which the compound in question is not just given directly to the bacteria.

Its first passed through an extract of the liver, usually rat liver, and it's in the liver where these detoxifying enzymes do their job, these cytochrome P450's that are referred to here are present in abundance in your liver. And so if mutagens are going to be formed, they should be formed in this in vitro extract.

And then, one takes the product of that and performs the bacterial mutation or reversion test. OK, and now the things that were carcinogens but not seen to be mutagens can be seen to be mutagens again. OK, but -- -- still -- There are still some truly non-mutagenic carcinogens.

And two examples are alcohol and asbestos.

These do not pass any mutagenicity tests that I'm aware of. But both of them are clearly linked to cancer development: alcohol in the case of liver, cancer, and head and neck cancer, and asbestos in the case of mesothelioma, the lining of the lung.

So these are not mutagens. So how did they promote cancer formation? Based on the mechanism that was suggested over here.

These agents cause irritation in tissues -- -- which results in tissue destruction, loss of cells -- -- and their replacement of those cells, cell replenishment.

So, it recruits a lot of cells to begin to divide when they normally or former smokers. wouldn't. So it results in increased proliferation, and the increased potential for mutation because - when cells divide. When they duplicate their DNA, there is an inherent risk of making mistakes. It's not an error-free process. So the more cell division there is, the more opportunity there is for error, and therefore, the increased risk of acquiring mutations and

becoming ultimately a cancer. OK, I want to take a couple of minutes talking about one really important environmental carcinogen, something that we get exposed to. And that is cigarette smoke.

I mentioned that benzoate pyrene is one of the important ingredients in cigarette smoke, but it's actually not the only mutagen. There are actually hundreds of mutagens in cigarette smoke. And this is the most important environmental carcinogen that we have in our environments. And it results in a large number of deaths per year. Tobacco smoke is responsible for a high percentage of the 175,000 people who die from lung cancer in this country each year. About 150 were either smokers

And the association between lung cancer and cigarette smoking is really striking. If you look here, the green line represents cigarette consumption in males from the beginning of the century, the 1900s, through 1960. And you can see it rapidly increased through availability and social acceptance and social trends. Smoking was really rampant in the society. And shortly thereafter, with about a 20 year lag, you could see that lung cancer risk increased dramatically as well, which is directly attributable to the cigarette smoke exposure.

It took time because cancers don't develop right away.

They develop over years, and so you need to get exposed to stuff over a long period of time. But eventually the lung cancer started to rise. And you could see the shape of the curves are virtually identical. You can also see that the smoking rate has dropped off a little bit in men, and actually has dropped off a little bit starting about 15 to 20 years ago with respect to lung cancers as well. So smoking cessation has an effect.

If you reduce the exposure, you can reduce your risk.

That's true of men. Women have not caught up yet.

Women started smoking later than men, about 20 years later, and their lung cancer rates followed, then, their increases in cigarette smoking with about a 20 year lag, and you can see now that lung cancer among women is still rising. And it recently passed breast cancer as the most common type of cancer deaths among women.

So lung cancer is a major disease and is directly related to smoking and smoking history. Surprisingly, given that fact -- -- still 47 million Americans smoke, in recent polls something like 26% of men and 22% of women, a remarkably high number. And if you go to other countries, the numbers are worse. So the message clearly has not been adequately delivered. But what is even more surprising to me was the results of a survey done in 2002 where high school students are asked whether they smoked.

What do you think? What percentage of American high school students smoke? Anybody? It was 28%; more than one in four smoke. And I've heard recently that the number is increasing since 2002. So, this very, very

detrimental agent which one controls oneself is clearly not going away and will lead to, unfortunately, the deaths of many of these individuals because of lung cancer. And by the way, it's not just lung cancer that smoking is a problem for: emphysema, heart disease, and other diseases as well. I read a statistic which was really shocking to me. Of that however many billions of people are present on the planet today, the 500 million of them will die early because of complications of cigarette smoking.

500 million people will live less than their full lifespans because of cigarette smoke. So, if you learn nothing else from this class, if you currently smoke, stop. And if you don't smoke, don't start. OK, that was my little sermon.

Hopefully it had some effect. And it provides a segue into -- -- the sources of the mutations that occur in genes during cancer progression. We've just been discussing exogenous, or environmental mutagens, cigarette smoke being one, some lead exposure being another, dietary carcinogens I mentioned, environmental pollutants like the dyes in the ponds and ash land. They are common. They do certainly have an effect, but there are probably somewhat overblown except for some light and tobacco smoke, and then these rare instances of high exposure to very, very toxic things.

A more common problem are replication errors, mistakes that your cells make in duplicating their DNA.

They put in the wrong base or they skip a base, or other errors take place during DNA duplication.

Your DNA can break inside of your cells as it gets moved around from place to place or because of an exposure to certain things from the outside. And then this can lead to translocations or deletions or other rearrangements. And I'll tell you later about how those can lead to cancer-causing mutations.

Defects in chromosome segregation, dividing the number of chromosomes properly between cells, is another problem. And I shown you an example of that.

Here you can see that the number of chromosomes is also wrong in addition to their structure. So, defects in chromosome segregation are a problem in cancer. Defects in DNA repair processes can then facilitate further mutations.

And various metabolic processes can produce mutagens insider cells like super oxide molecules which are very reactive and very mutagenic.

Your cells have ways of detoxifying, but they're not always perfect. You can also take antioxidants to try to reduce your risk of getting this kind of exposure. But nevertheless, these endogenously produced mutagens are another common source of mutations in cancer. So, we get exposed to things.

We produce things, we make mistakes, and in our cells, alterations occur in cellular genes which drive this process forward.

And overall, therefore, we observe a clonal evolution of more and more abnormal cells in the development of cancer.

And that's captured here. Clonal evolution from a normal cell, a cell that acquires a single mutation, this cell now has increased capacity to divide. So it divides more. More of its progeny are produced. We are maybe in the stage of hyperplasia here. And within this increased mass of cells, another mutation occurs. Now the cell has even greater capacity to divide or begin to act abnormally relative to its neighbors.

It begins to grow. And within this increased collection of cells, yet another mutation occurs.

There is a clonal evolution of more and more abnormal cells.

And we know that cancers, in fact, have acquired many, many changes in their DNA as evidenced by the chromosomes, but also as evidenced by our knowledge of the sequence of key genes that are affected in cancer. Now, as we'll discuss, many of these genes affect proliferation -- -- and cell death.

Again, cancer is a disease of cell number, too many cells.

And this process is normally very carefully balanced inside of your bodies inside of your tissues. There is an equal balance between proliferation -- -- and cell death so that in normal homeostasis -- -- you have the appropriate members of cells produced as die off, and so that ultimately you are in balance. But in cancer, the balance is shifted. It's shifted in the direction of proliferation, and away from cell death. And the consequences of that are that you've now produced too many cells for the tissue, too many cells in the gut, too many cells in the blood.

And these cells, then, accumulate and acquire additional changes that imbue them with those qualities that advanced malignancies have.

Increased proliferation is one thing, but importantly it's not the only thing. Increased proliferation and cell death are important qualities for sure. But also as I mentioned, cancer cells develop in other ways that are important in the development of malignancies.

Today, for example, a recruit a blood supply. They secrete factors that cause the blood vessels to grow into them, to feed the tumor.

They increased their motility. Cancer cells move around. They move into tissue. They move into the bloodstream.

They move back out again. And that's what this intravasation term means, moving into the blood supply, and other characteristics as well, how they remodel the extracellular matrix, or how they avoid the immune system, all sorts of things that cancer cells require in order to survive to get bigger, to thrive, are acquired through alterations in cellular genes. Now, the final thing, and I'll close with this and pick it up again next time, the final thing that convinces us that cancer is a disease of your genes is that we've now sequenced the genes of cancer cells and have found alterations. Like in this gene here that you've been exposed to, the RAS gene, in which in normal cells we see one sequence and in cancer cells we see a different sequence, and we can understand that as a change in the activity of this important signaling protein that causes cells to divide inappropriately. And I'll stop there.