Sarah, maybe we can start off by talking about lung cancer. I mean when many people think about lung cancer, they think of it as kind of a devastating disease.
in the US among both men and women. But you’re right, it absolutely can be a devastating illness and because of that, it’s the number one cause of cancer deaths among both men and women.

So it’s common, and it’s a common cause of death from cancer. But I think a lot has changed in recent years. I know we’ll talk about a lot of that, but some of the things that we’ve known for a long time now is that people tend to be older when they get lung cancer, although some people are quite young. Smoking is a risk factor for lung cancer, but again, some people have never smoked a day in their life and they can still get the disease. Does genetics play into it? I mean on this show we talk a lot about genetics as well, but when it comes to lung cancer, most of us think that this is really a smoking related cancer. Although as you say there are people who never smoked a day in their life who get lung cancer. So for them, is it really genetics? What’s an underlying
There’s a lot about lung cancer that we still don’t know. And your question is a great one, and it’s something that we still don’t fully understand about lung cancer because smoking is such a common risk factor for lung cancer. When we see someone who’s smoked, who gets lung cancer, we think that it’s probably related in some way. But again, when people have never smoked, we really don’t understand the cause for the vast majority of those cancers. When you think of genetics in terms of inheriting a gene from your parents or passing it along to kids, that’s not really common at all in lung cancer like it is in other cancers like breast cancer, which tends to be more common. We just don’t see that very much in lung cancer, so why some people who have never smoked get it is still really an outstanding question in the field. There are some other environmental risks, but much, much lower than the risk of smoking.
but again, much lower.
Radon is always a question.
There probably is some risk there,
but how to quantify that?
It is very difficult,
so for many people who haven’t
smoked or haven’t smoked much,
it’s still very unclear
why they get this disease.
You know the other thing
that we talked about in a lot
of different cancers is that any
particular cancer lung cancer,
breast cancer, colon cancer,
whatever, it is rarely one disease, is
lung cancer like that as well?
Or are all lung
cancers essentially the same?
So this is one of the things that
I think is the most interesting and
probably exciting about lung cancer.
Up until a couple years ago we really
thought there were two types of lung cancer,
small cell and non small cell lung cancer.
But over the last really 10 or 15 years
it’s become clear that it’s multiple
diseases that are all labeled as lung cancer because of where it started,
where the cancer started in the lung.
And this is one of the biggest advances
in the field over the last several years
The understanding of the different types of lung cancer and it’s not just so that we can define things in a different way. It’s really because it impacts treatment and how well different cancers respond to different treatments. How well someone is going to do with various treatments, and so differentiating these different types of lung cancers is absolutely critical so that we can get the best treatments for patients. How well someone is going to do with various treatments, and so differentiating these different types of lung cancers is absolutely critical so that we can get the best treatments for patients. We still do think about small cell and non small cell, but mostly within the realm of non small cell lung cancer is where we’ve been able to divide things up even more and understand mostly the molecular basis of lung cancer. Meaning that the cancer has different mutations and that is really part of what defines it. Now you just asked me about mutations and I said it’s not very common in lung cancer, but I’m talking about a different type of mutation here, so it’s not very common that people have a genetic predisposition to lung cancer. But finding mutations in the cancer itself is actually quite common.
other guests on the show here as well who talk about this concept where a biopsy is taken and the tumor is profiled for a number of mutations, genetic mutations that it could have that could tailor therapy and it sounds like lung cancer is in that realm as well.

Tell us more about the mutations that you look for and the sub classifications that you think about when you’re treating a lung cancer patient.

Lung cancer is a great example of a disease where the molecular classifications are so important, and so whenever we see a patient with a non-small cell lung cancer, that’s advanced meaning at stage four, it’s critical to get molecular or mutation testing.

People will call it different things. Molecular testing, mutation testing. Tumor profiling is sometimes used, and so that is now entirely a standard part of treatment and what’s really changed over the years is what we need to test and

when I first started in this field now 10 years ago there was really just one mutation that we can target
and that was the EGFR mutation and that was so exciting at the time because it was really the first time in lung cancer that we could get a biopsy as you say and do the mutation testing and if we found this mutation we had a great treatment which is a targeted therapy pill, EGFR inhibitor and that is still the case today where we’re looking for EGFR mutations and we will target those cancers with pills that treat that specific abnormality in the cancer. Some people will call it targeted therapy or precision or personalized medicine, but now instead of just one mutation that we can target, we have several that have been discovered in lung cancer that have associated targeted therapies. So we’ve really come a long way in just a couple of years where now we don’t test one, but we test many genes because we may be able to find a mutation that is important in that cancer. Tell us the other mutations that you look for. Thinking about a timeline, so ALK was probably the next one that was discovered.
ALk is a mutation in a gene that again can be part of a lung cancer, especially lung adenocarcinomas. Most of these mutations really all these mutations are mostly found in adenocarcinomas, which is a type of non-small cell lung cancer. And so ALK is another mutation like the EGFR mutation where if we find it I get very excited for patients because we have fantastic therapies for ALK. So that’s another one. It’s rare, ALK rearrangements are found in just a couple percent of lung cancers. But again, absolutely critical to look for because of the great options for treatment, we have another another gene that we always test is called RAS one, and that also can have a mutation in it and the list keeps going on. So that was really all we had for a couple of years. But really, in the last I would say year or two, there’s been even more of discovery of alterations, so now we always will need to assess for BRAF mutations. BRAF is a gene that commonly has mutations in Melanoma,
but more recently was also found to have mutations in lung cancers.  
Again just a couple of percent of lung cancers have BNRAF mutations, but now we have targeted therapies that we can use for that and then really recently within just the last couple of months or year we look at MET mutations and ntrk mutations, RET I might have forgotten a couple there’s getting to be so many.  
We have now several new FDA approvals for these targeted therapies, but if you don’t know the mutation is there, you’re not going to use the drug, so it’s really become very important to test even more than ever before.  
And you mentioned that this is standard, but you’ve mentioned now at least half a dozen mutations that you look for.  
So is that something that is standard of care?  
So any of our listeners, no matter where they go, whether they go to a large academic Cancer Center or whether they go to
a local private practice oncologist, is that something that is going to be tested for them for their lung cancer across the board and across the country? Or is this still something that really hasn’t found its way out of academe yet?

It absolutely should be standard of care because we have FDA approved therapies when you find one of these targets that aren’t useful unless the target is there and you don’t know to use it unless you find it so, this should be part of standard of care for every patient, no matter where they are.

The testing is available anywhere. We do the testing in house, so our pathology Department is fantastic. They do the testing here, but there’s companies that do this testing now, so it is available anywhere in the US. It’s a matter of whether it’s done, and I think that’s the bigger question, so I think now, because EGFR mutations have been part of the standard testing, you really have to test for EGFR mutations, and that’s been for 2004 was when the mutation was first discovered,
so we’ve known about EGFR mutations for well over a decade. I think that’s become very standard to test and then the other ones I mentioned, initially, Alk and RAS, those have become more common because they’ve been around for awhile too. But the other ones that I mentioned are equally important. The issue is that there are more recent so that sometimes things take longer to catch on, and they’re also really rare, so each one of the other ones I mentioned, are no more than 2% of lung adenocarcinomas, so they are rare but really important to test for, so I would hope and expect that they are being tested in every patient with an advanced form of adenocarcinoma, but I suspect that that’s not always happening because of the rarity of them, and because it’s a relatively recent advance in lung cancer, but they should be tested. Now we actually test for a whole lot of other genes at Yale, and I think that a lot of other academic centers,
so that part is maybe not as necessary.
You know, we test for at least 50 genes at Yale and some of that is trying to think about clinical trials for patients and other things, but those, as you said, more than half a dozen genes are standard care.
Obviously, important to test for and is that covered by insurance? I mean, is that expensive? I’m kind of trying to think of this from the standpoint of our listeners who may have lung cancer, who have been recently diagnosed and who may not have known to ask. You know what is my ALK status, you know? Do I have a RAS mutation and so you know, in broaching that subject, one of the issues that always comes up is number one, what is the cost and #2, is it covered by my insurance?
And then of course #3, can I really avail myself of the therapies? But we’ll get to the therapies part in a moment. What about the testing?
Is it expensive?
If people haven’t been tested, can they get their own specimens and send them off to some lab that can do a commercial test if they so wanted?
How does that all work?
Right, so because the testing and the treatment is standard of care and approved by the FDA, it’s covered by insurance, so these tests are expensive. It’s all genetic testing DNA sequencing things like that it’s covered it’s standard, so it’s covered by insurance.
So in terms of if someone could just go, you know, do their own testing, the nice thing is that once you’ve had a biopsy, it goes to the lab and it stays there for as far as I understand, decades. So if someone asked their oncologist, have I had this test and the answer is no. Actually we didn’t test for all these. It’s not like all is lost.
You can still test it. I think that has to be done from the doctor’s office and the pathology Department, but it absolutely could be done.
even years after a diagnosis is made. Well, we’re going to dig more into what happens after you have that information in terms of treatment, right after we take a short break for medical minute. Please stay tuned to learn more about lung cancer with my guest doctor Sarah Goldberg. Support for Yale Cancer Answers comes from AstraZeneca, an industry leader in the development of breakthrough immunooncology therapies across multiple tumor types and stages of cancer. Learn more at astrazeneca-us.com. This is a medical minute about Melanoma. While Melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. When detected early, however, Melanoma is easily treated and highly curable. Clinical trials are currently underway to test innovative new treatments for Melanoma. The goal of the specialized programs of research excellence in skin cancer, or SPORE grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improved diagnosis and treatment.
More information is available at yalecancercenter.org.

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Welcome back to Yale Cancer Answers.

This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Sarah Goldberg and we’re talking about lung cancer and right before the break Sarah was telling us about how lung cancer is actually a much more complex disease than we thought previously. No longer do we think about it just as small cell and non small cell but really, lung cancer has burgeoned into a whole plethora of diseases based on genetic mutations of the cancer itself that can be profiled and potentially targeted for therapies, while expensive, is covered by insurance. Sarah the one question I wanted to pick up on just before we move on to the treatments, which I think is going to be super interesting, is what about for our non insured uninsured patients? It’s great that the testing is covered by insurance, but if somebody doesn’t have insurance as many,
many American patients don’t, what are their alternatives? Yeah, lack of insurance is difficult in a lot of different ways, not just with testing. It also comes down to doctors visits and treatment too, so I think that’s something that we sometimes see and we work very closely with multiple people to try to work on these issues, especially our social workers and try to make every effort to get people the care that they need in whatever way possible, whether that’s helping them find insurance or figure out other resources because it’s such an important part of care to get this testing done. I think that kind of is wrapped up in the whole issue with diagnosis and then finding the right treatment. It’s all part of that. So typically were able to find a way to cover this in some capacity for patients.
We could do a whole show on all of the implications of having so many millions of Americans being uninsured, and what that does for the health of our nation, but that’s another show.

Let’s turn to a happier topic, which is now that we have an understanding of all of these mutations that every cancer can exhibit,

we now can figure out what makes one cancer different from another. And once we can figure out what makes a cancer tick,

we can potentially stop it from ticking through personalized therapies and targeted agents that can really address these pathways.

So can you talk a little bit about the exciting drugs that address each of these mutations?

Sure, so as you mentioned, there’s many different exciting drugs for the various mutations, and each one generally does the same thing.

It tries to block the activity of the abnormal mutation that’s causing the cancer to grow and be abnormal.
And if you could block that, it could be extremely effective, and so that’s true regardless of which of these mutations are found in the cancer. EGFR is a great example, because we’ve known about it for the most amount of time. There was an EGFR inhibitor that we used initially called erlotinib. But over the years we’ve realized that other EGFR inhibitors that have been developed since then are even more effective and seemed to work in more people and work for longer, because one thing that I haven’t mentioned is that these drugs, while they can be extremely effective and help people, and shrink the cancer and work for a long time when the cancer is at an advanced stage, it’s not curable so the drugs can work and again they can work for years. But at some point the cancer gets smarter and grows despite these targeted therapies. So as we’ve developed newer and better drugs, they tend to work for longer, and so that’s really what we’re trying to do is find drugs that work for a really long time and make this
Cancer is a chronic disease that people may not be able to cure or get rid of entirely, but they can live with it for a long time, and so in each of the different targeted therapy realms for each mutation we have great examples of drugs that can give people many more years of life than they otherwise would have had. And with each of these drugs, though there’s presumably side effects, what does that look like?

Any drug can have its share of side effects and it’s variable depending on the drug, but overall, the targeted therapies tend to have less side effects than kind of our classic cancer drugs, mainly chemotherapy because they’re targeted and aimed specifically at the mutation. That’s the abnormality in the cancer cells which doesn’t exist in other cells, in the normal cells in the body. The non cancer cells. The mutation is not there, so the drugs don’t tend to bother
the normal cells quite as much as with chemotherapy. So again, every drug is different. Some of the more common ones that we sometimes see is rash, sometimes people are more tired than they usually are, but generally they are much better tolerated. So it’s almost like a win-win. They work better than other cancer therapies, and they have less side effects, so again, we find one of these mutations that we can target in a patient. I am very excited and I think hopefully my enthusiasm catches on to the page with the patient and they get very excited too, especially once they see how well it works. Now you know when people are talking about therapies, clearly they’re really excited about these really effective therapies that last a really long time, but the other thing is that they don’t really want to come to the hospital and have an IV infusion of a therapy. And when people think about chemotherapy, that’s what they think about they think about being in the infusion suite.
0:21:36.376 –> 0:21:38.196 hooked up to an IV
0:21:38.2 –> 0:21:40.39 losing their hair and getting nauseous,
0:21:40.39 –> 0:21:41.96 and repeating that cycle
0:21:41.96 –> 0:21:44.81 multiple times, so are these therapies
0:21:44.81 –> 0:21:46.558 IV, or are they oral?
0:21:46.558 –> 0:21:50.64 How well do they fit into peoples lives?
0:21:50.64 –> 0:21:53.07 Especially if we’re talking about
0:21:53.07 –> 0:21:56.037 taking them for a long time
0:21:56.037 –> 0:21:58.252 and making what was previously
0:21:58.252 –> 0:22:01.329 thought of as a fatal disease,
0:22:01.33 –> 0:22:05.083 more of a chronic one that you can live
0:22:05.083 –> 0:22:09.11 with rather than die from.
0:22:12.166 –> 0:22:13.418 The IV treatments are challenging because
0:22:13.418 –> 0:22:15.554 people usually have to
0:22:15.554 –> 0:22:17.216 come in fairly frequently for them,
0:22:17.22 –> 0:22:18.942 and you spend time here instead
0:22:20.51 –> 0:22:21.88 These drugs are all pills,
0:22:21.88 –> 0:22:23.936 so that does make it a really nice
0:22:23.936 –> 0:22:26.359 part of it is that you take your
0:22:26.359 –> 0:22:28.945 daily pill or twice a day pill like you
0:22:28.945 –> 0:22:30.62 would take your blood pressure pills
0:22:30.62 –> 0:22:33.035 and you don’t need to come into the
0:22:33.035 –> 0:22:35.299 hospital nearly as often as an IV medicine.
0:22:35.3 –> 0:22:37.856 I will say that
0:22:37.86 –> 0:22:40.396 as exciting as all of this is,
0:22:40.4 –> 0:22:41.664 and hopefully you can
0:22:41.664 –> 0:22:43.244 sense my enthusiasm for it,
0:22:43.25 –> 0:22:44.814 it still is only
0:22:44.814 –> 0:22:48.17 maybe about 20 or 25% of patients
0:22:48.17 –> 0:22:50.77 with lung cancer that we can find one
of these mutations that we can target. So the numbers are going up as we find more mutations, but it’s still unfortunately not everyone and so there’s been a huge amount of work in other areas of lung cancer where we can’t find a targetable mutation, and then the other end that’s mainly with immune therapies. What about the other 75% of people? What’s in their cancer if they don’t have targetable mutations, and what can we do about that? So I think those two areas are so critical as well because we haven’t come far enough to figure out a targeted therapy strategy for every patient yet. And I think that both of those issues are are so critical. Let’s dig into those. But before we get there, these targeted therapies are, for example, in breast cancer we have targeted therapies as well, which often are given in combination with chemotherapy. But it sounds like these targeted therapies can be used as sole agents. Is that right?
That’s right. Yes. There is some research going on trying to combine them with chemotherapy, but you’re right at this point, the way we use them is the targeted therapy alone. They’ve been really in almost every case there’s been trials comparing the targeted therapy compared to chemotherapy, and it’s superior in all the cases. Again, when you have the target therapy compared to chemotherapy, and use the targeted therapy, it’s better than using chemotherapy, and we haven’t found a reason to combine it, although there again, is some research looking at if combining it is beneficial. The standard is to use the targeted therapy alone. It’s really nice for a logistic point of view and side effect point of view as well. Yeah, I mean that’s so exciting, it does kind of sound like if you’ve got one of these mutations, you can take a pill and have fewer side effects and a better outcome than being hooked up to chemo. And you can take your pills on vacation with you to wherever you’re going to go and live your life.
And it sounds like that is just so exciting in terms of an advance, but it does bring us to the question of what if you’re not in one of those lucky groups that has a known targetable mutation, you mentioned immunotherapy. You know we’ve talked on this show about immunotherapy a little bit, and I’d like to dig into immunotherapy for lung cancer. But the one thing that some have found is that for some cancers, they actually still will look for a checkpoint in order to use a checkpoint inhibitor just to see what people’s PDL1 status is. But in other cancers, that isn’t necessarily something that necessarily plays into whether or not you can use immune therapy. So how does it work in lung cancer? This has been a huge area of research over the last few years in lung cancer and other cancers.
not have one of those mutations that we were talking about before. Again, if you have one of the mutations targeted therapies are great options, but otherwise typically immune therapy is going to be some part of the treatment because of how effective it can be and your question about the PD L1 status in lung cancer is really important. So just like we get those mutation tests and it’s so important for patients to find the best treatment for them. It’s the same with PD L1 status. So PD L1 is not a mutation or gene like we were talking about with the other area in lung cancer treatments. But it’s a protein on the surface of cells of cancer cells or of immune system cells. But in lung cancer, we look at the cancer cells and that protein PDL1 can tell us if immune therapy is more or less likely to work. So it’s not a perfect test by any means. I’ve had patients where the PD L1 status is zero, which tells you it has a low chance of working. However,
they’ve done incredibly well with immune therapy, and sometimes it’s high and the drugs doesn’t seem to work, so it’s not a perfect biomarker. But we do use it as part of standard treatment in lung cancer, and so when I meet a new patient with lung cancer again at Stage 4, we always will check mutations in PDL1 because if someone has a high level of that PDL1 marker we think we might be able to get away with just giving immune therapy just like we were talking about with targeted therapy, how it’s nice to avoid the chemotherapy if you can. It’s the same thing with immune therapy with a high level of PDL1 there’s a high chance of the immune therapy working even on its own, so we will try that instead of giving chemotherapy. And so if you are PDL1 low and you don’t have another targeted over another targetable mutation, those patients are more likely to get chemotherapy, but they’ll still
get the immunotherapy as well. Therapy can work so well we will typically give it no matter what, unless there’s a contraindication. If someone has an underlying autoimmune disorder but yes, if someone has that low PDL1 status or we don’t know PDL1 status then we don’t think and this is based on several different clinical trials. We don’t think we can get away with just immune therapy on its own and it seems to be much more effective if you combine it with something else and that something else is a bit of a question mark in lung cancer. Until recently it used to be we would combine it with chemotherapy so people would get a combination of chemo and immune therapy. But more recently now based on several recent clinical trials, we’re actually combining two different immune therapies together. So avoiding chemotherapy, but combining the immune therapies. And that’s an area of future research that is currently ongoing. We have several different clinical trials at Yale looking at these different
combinations of immune therapy.
Really trying to get away from the chemotherapy if we can and using combinations of immune therapy to really try to beat the cancer and really try to improve patients quality of life and how long they are able to live.
Doctor Sarah Goldberg is an associate professor of internal medicine in medical oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.