Non-small cell lung cancer (NSCLC) accounts for about 80-85 percent of all lung cancers and afflicts about 180,000 people in the United States each year. Targeted therapies have proven to be effective in attacking specific aspects of the cancer cell, like growth factors or blood vessels that feed the tumor. Each year, tens of thousands of people are cured of NSCLC in the U.S., and HealthWell has been honored to assist patients receiving treatments.

*NSCLC: Targeted Therapies and Beyond* is a recently published series of articles that brings you the stories behind the research and celebrates the researchers and organizations committed to improving health care. Please accept this complimentary copy as our way of thanking you for your commitment to advancing medicine and improving patients’ lives.

A Series by [REALWORLDHEALTHCARE.org](http://REALWORLDHEALTHCARE.org)

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Breaking Down Lung Cancer
By Emily Burke, PhD, Director of Curriculum Development, BiotechPrimer.com

Editor’s Note: This article originally appeared in Biotech Primer Weekly. For more of the science behind the headlines, please subscribe.

The hit TV series Breaking Bad featured anti-hero Walter White, who starts out as a sympathetic character: a mild-mannered high school chemistry teacher with a nagging cough that turns out to be lung cancer. Money problems precipitated by costly treatments, poor insurance, and a modest salary push him to start cooking up meth to ensure the financial security of his family. The treatments succeed beyond his expectations, restoring his health long enough for him to become an unexpected meth kingpin.

Breaking Bad is a fictionally extreme example of the chaos that can arise from a lung cancer diagnosis. In fact, lung cancer is the leading cause of cancer-related deaths in the United States. Let’s take a closer look at the molecular causes, the different types, and some of the treatments available.

The Danger
While Walter White did not smoke cigarettes, 90 percent of those affected by lung cancer are smokers. Other causes of lung cancer include environmental or workplace exposure to carcinogens (known cancer-causing agents) such as radon, asbestos, or air pollution.

Smoking causes cancer because the inhaled smoke contains a range of chemicals, 70 of which are known to be carcinogens, including benzene, formaldehyde, methanol, and acetylene. Some carcinogens are genotoxic, meaning that they cause cancer by directly interacting with and damaging DNA. If that DNA damage occurs in a gene involved in regulating cell division, cancer may result. Non-genotoxic carcinogens have no direct interaction with DNA, rather they disrupt cellular structures and change the rate of either cell division or processes that increase the rate of genetic error.

Radon gas exposure can result in cancer because it is radioactive, and the high-energy radioactive particles given off as the gas decays can cause direct damage to cellular DNA. Radon gas is released from the normal decay of radioactive elements occurring naturally in soil and rocks. Radon is not considered dangerous because it is usually present at very low levels. However, it can sometimes build up to dangerous levels in well-insulated, tightly-sealed homes built on soil rich in uranium, thorium, or radium.
Asbestos used to be a common insulating material used in buildings and ships. The microscopic fibers in asbestos can be inhaled and become lodged in lung cells, triggering the activation of inflammatory pathways that result in the release of mutagens and factors that promote tumor growth. Since its hazards became well-documented in the mid-1970s, it is no longer used as insulation.

In addition to carcinogen exposure, there are likely genetic elements that make certain individuals more or less susceptible to lung cancer. Even though 90 percent of lung cancer cases are caused by smoking, only about 10 percent of smokers get lung cancer. In African-American populations, even when differences in smoking rates and access to healthcare are controlled for, the rates of lung cancer are higher. Both of these scenarios suggest that there may be genetic factors that make certain people more (or less) susceptible.

**Small Cell**

About 10 percent of lung cancer is small cell, meaning it occurs in the very small cells found in the bronchii—the tubes that branch off of the trachea, enter the lungs, and divide into even smaller branches within the air sac.

There are currently no targeted therapies available for small cell lung cancer, with chemotherapy and/or radiation as the main line of treatment. Broad ranging therapies that harness the immune system are in the pipeline.

**Non-Small Cell**

Cancer that occurs within any cell outside of small cells is referred to as non-small cell lung cancer (NSCLC), making up the majority (~90 percent) of lung cancer cases.

A number of drugs targeting new blood vessel growth—angiogenesis inhibitors—have been approved for the treatment of NSCLC.

There are also drugs that target specific NSCLC–associated mutations. For example, 10-35 percent of NSCLC cases are caused by the over-expression of the growth factor receptor EGFR. These types of NSCLC—more common in non-smokers—can be treated by drugs that target and inhibit this receptor. Asians are much more likely than other races to carry an EGFR mutation.

About five percent of NSLC cases are caused by mutations in a gene known as anaplastic lymphoma kinase (ALK). ALK proteins activate cell division, and mutated versions can drive cell division inappropriately. There are drugs currently on the market that inhibit ALK.

A checkpoint inhibitor drug has also been approved for NSCLC patients whose cancers start growing again after chemotherapy.
Cocktail Fodder: Walter’s Diagnosis
Diagnosed with NSCLC, Walter White specifically had an inoperable stage 3A adenocarcinoma. This means the cancer was initiated in the mucus-producing cells of the lungs and had spread to the lymph nodes (or other sites near the lungs), but had not spread to distant sites within the body. Some types of adenocarcinomas are caused by ALK mutations, so it is possible that Walter’s miraculous recovery was caused by an ALK inhibitor.

Read this article on Real World Health Care.
This week, Real World Health Care speaks with Jennifer King, PhD, Director of Science and Research for the Lung Cancer Alliance. The Lung Cancer Alliance is the leading and highest rated nonprofit organization dedicated to fighting lung cancer in the nation. Since 1995, it has played a critical role in every major advance — changing how people support, talk about, detect and treat the disease — and turning those impacted into survivors. Its mission is saving lives and advancing research by empowering those living with and at risk for lung cancer.

Real World Health Care: How does the Lung Cancer Alliance fund, or acquire funding, for the research it supports?

Jennifer King: Our funding for all our programmatic work, including our research platform, comes from a variety of sources. The majority is through individuals, private family foundations and corporate partnerships. On the research side of things, we also apply for grant funding, including through federal agencies like the National Cancer Institute.

RWHC: How does the LCA determine which research it supports, either through funding or through its advocacy work?

JK: Our research vision consists of six core areas: screening implementation, biomarker research, patient-powered research, enhancing clinical trial participation, survivorship, and increasing research capital. If a project or initiative fits in one of these six buckets, we will consider it for our portfolio. We don’t make direct grants; we work with researchers and other organizations to move projects forward through innovative partnerships.

RWHC: What is the LCA currently doing to promote and/or fund research into non-small cell lung cancer? What are your priorities in this area?

JK: We have funded a young investigator in partnership with the Conquer Cancer Foundation. Her work is currently focused on immunotherapy research for people with late stage NSCLC. We are also launching a clinical trials initiative to navigate more patients through the clinical trials process and enhance clinical research. There are so many emerging therapies in this area that more clinical
research is necessary to understand what the right treatments are at the right time for individual patients.

**RWHC:** What are the biggest challenges in NSCLC research and how is the LCA working to overcome them?

**JK:** A big challenge is the lack of research capital. We fund young investigators, as I mentioned, to support more people studying lung cancer. We also work with Congress to ensure the continued funding of the Lung Cancer Research Program with the Congressionally Directed Medical Research Program at the Department of Defense. To date, $102 million has been allocated for lung cancer research through this program.

**RWHC:** What would you say have been the most important advances in NSCLC treatment over the past 10 years?

**JK:** Without a doubt, the two biggest advances have been targeted therapies and immunotherapies. Targeted therapies attack a specific mutation in the cancer cells. This typically causes fewer side effects than standard chemo and truly personalizes the treatment plans for each person diagnosed. Immunotherapies use a patient’s own immune system to fight his or her cancer. There have been a number of new drugs in both fields that are offering more hope to patients, but a lot of questions remain about how to best use the new therapies.

**RWHC:** What do you think will be the next biggest advances in NSCLC treatment in the near future?

**JK:** We are on the horizon of understanding how to combine different types of NSCLC treatments and for whom. There are trials using immunotherapies and targeted therapies with each other, as well as with chemo, radiation, and surgery. A huge number of questions remain about how to use these drugs, for whom, and together or in what sequence. Understanding how the new agents do and don’t work together and being able to personalize the treatments for each individual cancer will lead to major changes in how we care for NSCLC patients. There are also exciting new advances in fields like nanotechnology and health information technology that may someday have a broad impact on cancer care.

**RWHC:** Why did you get into this field in the first place? What continues to inspire you about it?

**JK:** I have always been interested in the science of how disease works and how we can potentially use that knowledge to help patients. This started back in high school when I did a biology project on gene therapy. I’m a former cancer researcher, but I joined Lung Cancer Alliance in early 2015 because I was excited about seeing how the science was impacting the patients themselves.

It’s been such an inspirational 18 months. We had six new drugs approved in 2015 for lung cancer, and there’s many more on the way. The science is constantly changing as we keep learning, which keeps the work interesting. Now, I get to talk with patients, respond to questions and understand the
issues that matter most to people living with lung cancer. It’s a constant inspiration to keep pushing for new and innovative research studies that will help patients and their families.

Read this article on Real World Health Care.
American Lung Association: Research Focused on Improving Patient Care and Saving Lives

As part of our series on non-small cell lung cancer (NSCLC), Real World Health Care spoke with Susan J. Rappaport, MPH, vice president for research and scientific affairs, American Lung Association. Rappaport provides leadership and direction in the development and implementation of the American Lung Association public health education and research programs. She works with leading scientists to develop research and scientific policies relevant to lung disease.

Here, Rappaport shares insights on how the American Lung Association supports research for NSCLC and other types of lung cancer.

Real World Health Care: How does the American Lung Association fund, or acquire funding, for the research it supports?

Susan Rappaport: The American Lung Association has been funding research for more than 100 years. We receive our support through public donations, including our annual Christmas Seals® campaign, Fight for Air Climbs and LUNG FORCE Walks. We have a long history of connecting with people and communities in support of lung health.

Our organization was founded in response to tuberculosis — the most feared disease at that time. Now, with tuberculosis largely controlled in the United States, we have turned our sights toward defeating lung cancer and working toward a world free of lung disease.

Research is a critical part of our LUNG FORCE initiative, which focuses on lung cancer in women, to raise awareness and more lung cancer research funds. Through LUNG FORCE, we have already invested an additional $1 million in lung cancer research. The Lung Association’s Awards and Grants Program supports a rich array of studies in lung cancer to help improve methods of early detection and develop better treatment options for patients. In the past four years, we have funded more than $4 million in lung cancer research grants and have doubled our investment in lung cancer since 2015. This year, the Lung Association is funding more than $6.5 million in lung disease research.

RWHC: How does the Lung Association determine what research it supports, either through direct funding or through its advocacy work?
SR: It is important to the Lung Association that we fund the best projects available on a host of lung disease issues. We solicit grant applications each year, and successful applicants are identified through a scientific peer review committee system modeled on the one used by the National Institutes of Health (NIH). These peer review committees are comprised of accomplished and diverse researchers with the necessary expertise to review and assess each proposal. Proposals are funded based on the results of this process, ensuring that we only fund those applications considered of the highest quality, and with the best chance to advance our understanding of diseases, improving patient care and ultimately saving lives.

We know our chances of significant improvement in patient lives and of finding a cure increase when we work together. That’s why we collaborate with other organizations and advocate for increased research funding at NIH.

RWHC: What is the Lung Association currently doing to promote and/or fund research into NSLC? What are your priorities in this area?

SR: Our overall priority is to fund the best research that has the greatest chance of a scientific breakthrough and making a difference in patient care and quality of life. With increased funds available to lung cancer researchers, we attract and retain brilliant, motivated investigators to the field.

As NSCLC accounts for 85 percent of all lung cancer cases, many of the proposed projects do focus on this specific issue. However, the nature of scientific discovery has shown us that answers from one area of research can also work more broadly. Areas that drive our lung cancer research — all of which can address NSCLC — include:

- Development of new and combination therapies
- Biomarker discovery and validation
- Targeted therapies and resistance
- Screening implementation and novel screening for the non-high-risk population
- Lung cancer initiation and growth

RWHC: What are the biggest challenges in NSCLC research and how is the Lung Association working to overcome them?

SR: Among our biggest challenges is to be able to fund all the qualified research applications we receive. Each year, we turn away qualified researchers and projects due to the limited availability of funds. LUNG FORCE seeks to raise additional funds for lung cancer research and raise awareness about lung cancer as the leading cause of cancer deaths. Again, we strive to overcome gaps in funding by leveraging our resources, collaborating with other organizations and advocating for increased federal funding for lung cancer research.

RWHC: What would you say have been the most important advances in NSCLC treatment over the past 10 years?
Scientists have discovered somatic mutations — called “driver mutations” — that drive the development of lung cancer. These discoveries, made over the past decade, have transformed how to identify and treat the disease. Now, lung and other tumors can be tested for these mutations. There are now specific therapies that can address those genetic changes that keep the cancer cell growing. These therapies target the mutations in different ways, are more specific and have fewer side effects. These advances in precision medicine have led to lifesaving discoveries and treatments.

Another sea change in lung cancer treatment is immunotherapy. Cancer cells have found ways to keep the immune system from identifying and destroying them, as they do for infectious invaders. Immunotherapy medicines work to activate a person’s own immune system to recognize and kill cancer cells. So far, immunotherapy has only been approved to treat some forms of NSCLC. Currently, only a minority of patients respond to immunotherapy. However, a large proportion of those who do respond have improved survival.

What do you think will be the next biggest advance in NSCLC treatment in the near future?

Our scientific advisors believe that the Lung Association should invest in the following areas, which they identified as having the potential for the most important breakthroughs — all of which can apply to NSCLC:

- Additional precision medicine in treatment of early-stage lung cancer
- Precision medicine to identify patients who would benefit from newly developed lung cancer screening, irrespective of smoking history
- Non-invasive biopsy strategies
- Comparative effectiveness studies to improve clinical outcomes and cost-effectiveness after treatment

Does the Lung Association’s LUNG FORCE research innovation project address NSCLC?

This award will address all types of lung cancer. To better understand the impact of lung cancer in women, the American Lung Association has created a new research award to examine gender differences in lung cancer. Sharad Goyal, MD, is the first-ever recipient of the LUNG FORCE Research Innovation Project: Lung Cancer in Women Award.

Dr. Goyal’s project focuses on ionized radiation exposure during common cardiology procedures and how that affects the risk of developing lung cancer for women. The project leverages two large population-based data sets that include both cancer and cardiac information. Through analyses of these data sets, Dr. Goyal will evaluate the factors influencing the relative risk of developing lung cancer in a diverse group of people after this type of radiation exposure. This has not been previously studied, and it will take two to three years to complete the analysis.

Read this article on Real World Health Care.
Non-Small Cell Lung Cancer: With Greater Understanding Comes Greater Challenges

This week, Real World Health Care speaks with lung cancer specialist, Gregory Masters, MD, FASCO, attending physician at the Helen F. Graham Cancer Center and associate professor at the Thomas Jefferson University Medical School. In addition to being Fellow of the American Society for Clinical Oncology, Dr. Masters is co-chair of the ASCO Committee for Updated Guidelines on Chemotherapy for stage IV non-small cell lung cancer. We talked about some of the challenges facing both researchers and clinicians treating patients with non-small cell lung cancer (NSCLC).

Real World Health Care: What do you see as the biggest challenges facing NSCLC researchers, and how can those challenges be overcome?

Gregory Masters: The field of lung cancer treatment is exploding in terms of our ability to understand the molecular biology of NSCLC, immunotherapies, targeted therapies and surgical techniques. We’re improving our ability to treat the disease, but we’re also challenged in terms of clinical trials. There’s a limited amount of time, limited number of patients and limited resources to design and implement those studies. More treatments mean more ways to design trials to compare and evaluate the efficacy of those treatments. So in some senses, the field is a victim of its success.

Collaboration is key, and the Cancer Moonshot program is a great example of this because it focuses on the pooling of data and resources to improve our ability to tackle the many challenges we face. We need the large cancer centers working together with community oncologists and the pharmaceutical industry to design studies, get patients enrolled and evaluate results.

RWHC: What do you see as the biggest challenges facing NSCLC clinicians, and how can those challenges be overcome?

GM: As our understanding of the biology of NSCLC increases, it adds a level of complexity for oncologists to keep up with. This is an issue that becomes more acute when you consider that the same oncologists treating NSCLC are treating other types of cancers as well, and there has been an equal explosion of research in other cancers.

We need to make sure that practicing oncologists have the resources they need for ongoing education. They need to attend relevant meetings and stay up on the latest research. They need to
avail themselves of the resources available through the National Cancer Institute. They also need access to clinical trials. The real-life challenge in all of this is finding the time and energy to keep up with the latest research and opportunities. In all honesty, there are often not enough hours in the day.

**RWHC:** What do you think have been the most important advances in NSCLC research over the past decade? And how are those research advances changing the face of clinical treatments?

**GM:** The biggest advances have been in our understanding of the molecular biology and molecular genetics of NSCLC, which allow for targeted therapies. Each targeted therapy has a targeted population, which helps us make good on the promise of personalized medicine. Plus, we now have immunotherapies that allow us to “turn off” immune system regulators. In a practical sense, this means that patients who, until recently had few options if they were coming to the end of the line in terms of the ability of chemotherapies to treat their disease, now have new clinical options. Those options not only increase our ability to treat the disease, they give our patients the emotional boost they need to take the next step.

**RWHC:** Where do you see NSCLC research going in the next decade?

**GM:** It’s hard to predict. I don’t think anyone would have predicted ten years ago where we are today. But one area of promise is the further characterization of molecular changes in tumors as well as secondary changes in patients who have mutations, such as ALK mutations. This work is exciting and just in its infancy. Another area of promise is in our understanding of the immune system to determine which patients will benefit from a course of treatment and which won’t. We’re also developing a better understanding of the importance of palliative care and quality of life. All cancer patients can benefit from palliative care, but we need to expand the care team to include more people who can help, especially because oncologists are stretched so thin. We need additional resources to help our patients manage their symptoms and provide for a better quality of life.

**RWHC:** While exposure to cigarette smoke, asbestos and certain chemicals have been linked to NSCLC, many patients have not experienced such exposures. At the same time, other people with high exposure don’t get lung cancer. Does this mean the disease may be linked to genetics or some other factor?

**GM:** This is a question we’ve been asking for many years. How do we differentiate between environmental factors and intrinsic risk in a patient or a population? It’s the old nature versus nurture debate. We’re certainly improving our understanding of risk factors, but we still do not yet know why some people have a higher risk while other who smoke two packs a day don’t. We need more research in epidemiology and population-based studies. Unfortunately, those studies are hard to do.

**RWHC:** Why did you get into this field? What continues to inspire you?
GM: Choosing a career can be tricky. I was exposed to some great role models when I first started studying medicine and developed a deep respect for oncologists and the relationships they have with their patients. I continue to have great interest in research and learning more about cancer, but more than that, I enjoy having a positive impact on my patients—seeing them improve and seeing the gratitude of family members who appreciate what I do to help their loved ones. That’s what makes me excited to come to work every day.

Read this article on Real World Health Care.
NSCLC: The Promise of Immunotherapy

As part of our series on non-small cell lung cancer (NSCLC), Real World Health Care spoke with Hossein Borghaei, DO, in the Department of Hematology/Oncology at Fox Chase Cancer Center, which is part of the Temple Health System. Dr. Borghaei serves as Chief, Thoracic Medical Oncology; Director, Lung Cancer Risk Assessment; and Associate Professor. He specializes in endobronchial disease, lung cancer, lung metastases, mesothelioma and thymoma and conducts research in molecular therapeutics.

Dr. Borghaei was the lead investigator of the CheckMate 057 study, which helped to introduce a new immunotherapy paradigm in lung cancer treatment.

Real World Health Care: Tell us about your role at Fox Chase Cancer Center, especially as it relates to the research and treatment of non-small cell lung cancer (NSCLC).

Hossein Borghaei: I’m a medical oncologist by training, with a special concentration in lung cancers. I treat patients at all stages of the disease and have run a number of clinical trials. Some of those trials have been investigator-driven, while others have been funded by the industry. I’m also involved in the Eastern Cooperative Oncology Group which does NCI-funded translational and clinical research. I also have a small research lab that does pre-clinical investigations, working with other investigators to find new ways to treat cancer patients with new or existing drugs.

RWHC: Can you share some highlights of your recent NSCLC research?

HB: The most interesting, impactful and attention-getting study I’ve been involved with recently is related to immunotherapy. This was a Phase III study in which we found that non-squamous NSCLC patients can live significantly longer with an immunotherapy drug called nivolumab than they can with single agent chemotherapy. The immunotherapy treatment has been approved, allowing physicians to use it to manage patients when there is a progression of the disease after platinum doublet chemotherapy. We also found that this immunotherapy resulted in fewer grade 3 or 4 adverse events.

We recently presented a follow-up to the study in which we found that, after a two-year time point, nearly double the previously treated non-squamous NSCLC patients and nearly triple the previously treated squamous NSCLC patients were alive compared with those treated with chemotherapy.
RWHC: What do you think are the biggest challenges in NSCLC research?

HB: We need more funding. NSCLC is a disease that affects a large population. It’s the number one cause of cancer deaths in the U.S. and it’s a very difficult disease to treat. Having adequate funding to study NSCLC is important. There are a number of drugs being investigated to treat NSCLC, so we also need patients who can participate in rationally designed clinical trials that can address specific questions and help to bring new treatments to the marketplace. There is certainly a tremendous amount of interest in evaluating new treatment options, but investigators running clinical trials are struggling in some cases to find the right patient population to study.

RWHC: What do you think are the biggest challenges relating to current NSCLC treatment?

HB: One of the biggest challenges relating to treatment comes back to the ability of patients to participate in clinical trials. Many trials are conducted in academic centers like Fox Chase Cancer Center, making it difficult for patients in remote geographic areas to participate. Even for patients who live close to a clinical trial location, they may have co-morbidities such as emphysema or COPD, making it physically challenging to participate.

Another challenge we face as clinical researchers is our ability to obtain biopsies from NSCLC patients. Biopsied tissue from tumors at different phases of the disease is critical for our ability to understand why some treatments work on some patients but not on others, and every biopsy has its risks. I’m hopeful that the emerging field of liquid biopsy — which will allow us to do molecular-level testing on blood samples — will help us overcome this challenge.

RWHC: What do you think have been the most important advances in NSCLC treatment over the past decade?

HB: Molecularly targeted therapies that allow clinicians to personalize cancer treatments have been successful for about 25 percent of lung cancer patients. Our ability to understand what’s going on in a tumor at a molecular level lets us better target specific drugs to treat and manage the disease.

RWHC: Why did you get involved in this field?

HB: As an oncology clinician, I really get to know my patients on a personal level. A cancer diagnosis is life-altering, and as a treating physician, I get to address my patients’ concerns and fears. I find that closeness extremely rewarding. From a research standpoint, there is such a huge need to understand the disease process and so many patients that we can’t yet cure. I want to contribute to our overall understanding of this disease and why it’s so difficult to treat. The research opportunities in NSCLC are almost limitless.

Read this article on Real World Health Care.
NSCLC: Targeting What Drives People’s Cancer

This week, Real World Health Care talks with Edward B. Garon, MD, Associate Professor of Medicine at the David Geffen School of Medicine at UCLA Health. He specializes in hematology and oncology, with an interest in lung cancer and chest malignancies.

Dr. Garon’s research focuses on the testing and development of targeted therapies and immunotherapies in the treatment of non-small cell lung cancer (NSCLC), including the development of a class of drugs known as PD-1 (programmed cell death-1) inhibitors, which allow immune cells to eliminate cancer. We spoke with Dr. Garon about checkpoint inhibitors, immunotherapies and targeted therapies for NSCLC.

Real World Health Care: Describe your role at UCLA's David Geffen School of Medicine, especially as it relates to research of non-small lung cancer.

Edward Garon: I serve as director of thoracic oncology and conduct both clinical and laboratory research with a focus on translational research to determine lung cancer patient subgroups that are most likely to respond to certain therapies. Instead of looking at NSCLC as one disease, it’s important to personalize therapy and give people the therapies that are appropriate, not just for the disease site origin, but for a disease that’s driven by a particular set of molecular events.

RWHC: What do you think are the biggest challenges relating to NSCLC research and how are those challenges being addressed?

EG: We’ve seen some real progress in NSCLC research, especially in terms of immune checkpoint inhibitors, which unleash a patient’s own T cells to kill tumors. But we’re not yet where we want to be. One of the biggest priorities is identifying more people who will respond to therapies and connecting the right research with the right patient population, especially since targeted therapies currently only apply to a small percentage of the patient population. Although early-phase lung cancer studies in non-metastatic patients have hinted at the potential to use biomarkers to select patients, data from clinical studies have tempered expectations.

RWHC: What do you think are the biggest challenges relating to current NSCLC treatment and how are those challenges being addressed?
EG: In the past 10 years, there has been a push to individualize care for NSCLC, to evaluate individual tumors on individual patients and determine if there are molecular changes or abnormalities in the tumor itself that can dictate whether there are certain therapies that are more or less likely to be effective in any given patient. Treatments for NSCLC have improved somewhat over time, but in patients whose tumors have progressed during or after their initial therapy, the outcomes for additional treatment have been quite poor.

Another challenge for clinicians is the emergence of checkpoint inhibitors, immunotherapies and targeted therapies. We currently have two PD-1 inhibitors available for treating advanced NSCLC, both of which are well-tolerated among patients. The quality and duration of responses to anti-PD-1 therapy can be profound in NSCLC, but some clinicians are not overly familiar with them and how to use them. Much of the experience with these drugs is concentrated in select academic centers. We need wider clinician awareness of which patients are most likely to benefit from therapy, when therapy should be stopped and how toxicity should be managed.

RWHC: Where do you think the biggest opportunities for future advances in NSCLC research and treatment lie?

EG: We will soon see a tremendous amount of data on the combination of checkpoint inhibitors and additional agents. It will be interesting to see both what the data from randomized studies show and how researchers interpret that data in terms of what constitutes a signal and what doesn’t. Careful selection of patients, doses of each agent, and information supporting strategies — concomitant or sequential — is still needed. Another exciting avenue is the potential incorporation of immunotherapy in early-stage disease, locally advanced disease and in first-line therapy for metastatic disease. These agents could become the frontline choice for select patients with stage IV disease versus standard chemotherapy.

RWHC: Why did you get into this field and what continues to inspire you about it?

EG: I became involved in lung cancer as a young physician coming from fellowship training. While there was not a lot of excitement in the field at that exact moment, I saw a good opportunity to be on the leading edge of therapy development. I am fortunate here at UCLA to be part of many of the studies of new drugs that have changed the course of patients’ disease and don’t have the toxicity associated with many chemotherapies. It’s certainly been gratifying to see how new therapies can positively impact patients. Just a few short years ago, NSCLC was seen as a disease that wasn’t particularly immunogenic. Ten years from now, I hope to look back on this exciting time and realize that we have come much farther still.

Read this article at Real World Health Care.
Non-Small Cell Lung Cancer: EGFR Mutations and Targeted Therapies

Continuing our series on non-small cell lung cancer, this week Real World Health Care speaks with Lecia V. Sequist, MD, MPH, Associate Professor of Medicine at Harvard Medical School and the Mary B. Soltonstall endowed chair in oncology at Massachusetts General Hospital. Dr. Sequist’s research focuses on studying novel targets and targeted agents for lung cancer treatment, particularly those that target the epidermal growth factor receptor (EGFR) and in detecting and studying the significance of tumor cells circulating in the bloodstream.

Real World Health Care: Tell us about what you do at Massachusetts General Hospital, especially in relation to research and treatment of non-small cell lung cancer.

Lecia Sequist: I’m a medical oncologist with a busy practice, seeing and treating patients with lung cancer. I also conduct clinical and translational research on new drugs, looking at the molecular aspects of tumors and biopsies as patients go through various forms of treatment. My focus is on personalizing treatment for each patient.

RWHC: Can you share some highlights of your recent research in non-small cell lung cancer?

LS: Most of my recent research has revolved around EGFR mutations. One of the biggest advances in lung cancer in recent years is that we’ve come to understand lung cancer is not one disease. It’s many diseases. We can now tell the difference between one cancer and another by looking at the tumor genetics. These are not the genes we inherit from our parents, rather they are genes that reside only in cancer cells. These genes are at the core of what causes cancer. By identifying these genes in a lung cancer patient’s tumor, we can be more successful with treatments that target those genes and the proteins they produce.

EGFR mutations were first discovered here at Mass General, right around the time I started in oncology. It was a very exciting time, and ushered in a new era of personalized treatment for cancer. Since those early days, we’ve done a tremendous amount of research with patients who have the EGFR mutation, and we’ve found treatments that work better than standard chemotherapy.
RWHC: What are some of the biggest challenges you face as a researcher studying non-small cell lung cancer?

LS: I think of the challenges in two categories: scientific and societal. From the scientific point of view, we can’t currently identify mutations in every lung cancer, though we’re constantly working to uncover more of them. The group of lung cancer patients who have no identifiable mutation, or who have a mutation with no matching drug therapies at this time, are effectively left out of the “molecular revolution.” For those groups, the challenge is to find alternative approaches. Luckily some of the newer immunotherapies may work particularly well in such patients. Then down the road, we know that targeted therapies eventually “wear off,” in the sense that cancer cells get smart and find ways to work around the roadblocks we put in their path. For example, we saw this with the first generation of tyrosine kinase inhibitors (TKIs) developed to target EGFR mutations. Most patients initially responded, but subsequently developed a resistance after about a year, because they developed a second mutation that prevents the TKIs from binding to the cancer cells. Last year, a new EGFR drug was FDA approved that is able to effectively target this second mutation. Now we’re racing trying to learn how the cancers may get around the newer drug and also looking at strategies to prevent resistance.

From a societal standpoint, one of our biggest challenges in the lung cancer research community is the stigma that still exists around lung cancer. In the United States, we were fortunate to have had a very successful public health campaign around the dangers of smoking over the last generation. Those dangers are important to understand, but one of the unexpected consequences of this was to popularize the opinion that lung cancer is a self-inflicted disease and therefore patients carry some degree of blame. Not only does this end up negatively affecting individual patients, it also cuts into research funding. The fact is, some smokers get lung cancer while others don’t. And more importantly, many lung cancer patients have never smoked. No one deserves lung cancer and research must push forward to stop this, the deadliest of all cancers.

RWHC: What are some of the biggest challenges you face as a clinician treating patients with non-small cell lung cancer?

LS: There are promising treatments being studied in clinical trials, but many patients don’t have access to those treatments because the trials are concentrated in academic centers. Even if patients have geographic access to research studies, clinical trials have fairly high thresholds for eligibility, so if a patient has other medical conditions — which many lung cancer patients have — or if their cancer has certain characteristics, they won’t be eligible for the trial. We need to keep pressure on the pharmaceutical industry to include broader groups of patients in trials so all patients can get access to promising new treatments.

RWHC: What do you think are some of the biggest opportunities for advancement in how we research non-small cell lung cancer and treat people with the disease?
**LS:** Immunotherapy has really changed the paradigm for non-small cell lung cancer. Years of failed vaccine studies led us to believe that it wasn’t possible to affect the human immune system in meaningful ways against lung cancer. Now that we’ve hit upon a different way to activate the immune system, new discoveries are tumbling out the door every day. Unlike past treatments, immunotherapy has true promise for long-term disease control. There are already three FDA-approved lung cancer immune therapy treatments over the last year and likely many more to come. I think someday we’ll look back on this time and say that this is when the needle really started to move.

**RWHC:** Why did you get into this field of research? What continues to inspire you?

**LS:** I was initially drawn to studying lung cancer when I was in training by the doctors who were mentoring me and the patients I met. At the time, there weren’t many treatments available for non-small cell lung cancer, so there was a lot of room for improvement. This was attractive to me as a clinician and a researcher and it has remained a vibrant and ever-changing field. I enjoy being involved in the exponentially increasing number of treatments available and how these new treatments can bring hope to patients. It has ended up being an intellectually stimulating and extremely fulfilling career and I continue to be inspired by the patients I meet every day.

Read this on Real World Health Care.
**NSCLC: The Emerging Role of Liquid Biopsies**

Real World Health Care concludes its series on non-small cell lung cancer by speaking with Erica Carpenter, MBA, PhD, Research Assistant Professor in the Department of Medicine at the Perelman School of Medicine at the University of Pennsylvania. Dr. Carpenter also serves as Director of the Circulating Tumor Material Laboratory in the Division of Hematology/Oncology at the Abramson Cancer Center.

Dr. Carpenter served as senior author on a recent study that suggests for patients with advanced lung cancer, a non-invasive liquid biopsy may be a more effective and suitable alternative to the gold standard tissue biopsy to detect clinically relevant mutations and help guide the course of treatment.

**Real World Health Care:** Explain your role at the Perelman School of Medicine.

**Erica Carpenter:** I am Director of the Circulating Tumor Material Laboratory and an Assistant Professor in the Division of Hematology-Oncology at the Perelman School of Medicine. My lab focuses on the identification, capture, and analysis of Circulating Tumor Cells (CTCs) and cell-free DNA (cfDNA), exosomes and other material shed from cancer patient tumors. Blood, bone marrow, pleural effusions, and other non-invasively captured patient samples are used to detect biomarkers which will allow: early detection of disease as well as post-therapy monitoring of minimal residual disease, an efficient means of determining clinical and biological response to therapy and, thus, clinical decision making, and cancer genetic phenotyping to drive personalized medicine that obviates the need for serial biopsies in a population of patients for whom these procedures can be difficult, risky, and insufficient.

**RWHC:** Can you give us an overview of your recent research as it relates to non-small cell lung cancer and liquid biopsies?

**EC:** While the work described in the Clinical Cancer Research paper is the only NSCLC liquid biopsy study we have completed, we have several studies currently enrolling, including studies on the use of liquid biopsies to monitor and predict response of patients receiving a form of immunotherapy known as checkpoint inhibitors, and characterization of the tumor cells and circulating tumor DNA found in the pleural effusions (excess fluid that sometimes builds up in patients’ lungs) of lung cancer patients as another method for monitoring without an invasive biopsy.
**RWHC:** Just a few months ago, the FDA approved the first liquid biopsy test for patients with metastatic NSCLC. Why is this an important development?

**EC:** This is important for a number of reasons. First, the cobas test detects mutations in a gene called EGFR that can be targeted with specific drugs that have been shown to be effective in NSCLC patients with these specific mutations. In addition, liquid biopsies in general can greatly improve sensitivity of mutation detection in metastatic patients. Metastatic disease means that a patient has tumors in multiple sites in the body, and this can make surgical biopsy or fine needle aspirate very difficult to perform without great discomfort to the patient. Metastases can sometimes occur in places like the bone or brain where it is impossible to invasively obtain tumor tissue. Moreover, the genetic profile of a tumor tends to evolve over the course of a patient’s therapy, and it is not unusual for a metastatic patient to exhibit mutational heterogeneity where not all mutations are expressed in all tumor locations. In these cases, it is thought that a liquid biopsy will detect all or most mutations as all tumor sites, whether primary or metastatic, are thought to shed DNA into the blood. Finally, when a next-generation sequencing panel, such as the one used in our study, is applied to a liquid biopsy, comprehensive and clinically actionable data can be obtained with a single blood test, including mutations in multiple genes associated with therapy resistance.

**RWHC:** Do you think that liquid biopsies will become a standard of care for NSCLC patients? Will they, or should they replace tissue biopsy? Why or why not?

**EC:** Liquid biopsies are already becoming a routine part of care for NSCLC and other cancer patients here at the Abramson Cancer Center at Penn Medicine. These tests can be incorporated into the blood draw procedure for other standard of care monitoring blood tests and performed at already scheduled outpatient visits, thus causing no additional pain or inconvenience to the patient. We are working to better understand the different ways in which liquid biopsies can be used to better manage the care of these patients. However, while I expect liquid biopsy use for NSCLC and other cancer patients to continue to expand, I do not expect that they will replace tissue biopsy. Next-generation sequencing of circulating tumor DNA cannot provide crucial phenotypic information, such as information about the physical characteristics of the tumor, that are essential for initial diagnosis. Tissue biopsies can also play a unique role in monitoring of patients for the development of neuroendocrine disease, which can be associated with therapy resistance but is not detectable using ctDNA.

**RWHC:** What challenges need to be overcome to make them a standard of care?

**EC:** More studies need to be done, and this is an area of active focus for us, to measure whether the use of liquid biopsies has a positive effect on patient outcomes. In addition, clinical ctDNA tests tend to be ordered for detection of mutations that can be therapeutically targeted, or the emergence of mutations that signal the development of therapy resistance. To become a larger part of the standard of care for NSCLC and other cancer patients, we must better understand whether liquid biopsies can be used to effectively monitor patients receiving other important forms of therapy, including recently approved types of immunotherapy.
RWHC: This approved liquid biopsy test detects a specific type of gene mutation that is present in about 10-20 percent of NSCLC patients. Do you think other liquid biopsy tests will eventually be able to do the same for the remaining 80-90 percent of NSCLC patients? If yes, where does the biggest opportunity exist? If no, why not?

EC: In our study, we detected 275 mutations in 45 different genes, with at least one alteration found in the liquid biopsy for 84 percent of patients. Further underscoring the clinical utility of such a comprehensive liquid biopsy approach, 70 percent of patients were deemed to have a relevant clinical trial available on the basis of their ctDNA result, 55 percent of patients had an off-label targeted therapy that could possibly be used, and 31 percent of patients had an FDA-approved therapy available. So, I would say that liquid biopsy tests are already providing meaningful results for the majority of NSCLC patients.

RWHC: Beyond detecting the gene mutation responsible for NSCLC, how can liquid biopsies be used to monitor the progression of the disease?

EC: As I mentioned earlier, circulating tumor DNA tests for NSCLC patients are typically used to detect driver mutations and/or mutations that indicate the development of therapy resistance, some of which can also be therapeutically targeted. However, sometimes the physical characteristics of the tumor, including the number of circulating tumor cells in blood and expression of certain protein markers, can be measured by liquid biopsy and used to monitor disease progression. For instance, an increase or decrease in the number of circulating tumor cells (CTCs) detected in a tube of blood can be an indication of disease progression or response to therapy, respectively. Moreover, these CTCs can be isolated and gene expression measured to detect signatures associated with sensitivity or resistance to certain forms of chemotherapy in other cancers. CTCs can also be used to non-invasively assess expression of a protein known as PDL-1 which has been shown to be associated with a response to a form of immune therapy known as checkpoint inhibitors.

RWHC: How can NSCLC liquid biopsy tests be used to help increase the length of NSCLC patient survival?

EC: This is an area of active study for us. We will seek to measure whether repeat, non-invasive liquid biopsies can be used to detect therapeutic targets when a tissue biopsy isn’t possible, thus possibly enhancing the chance of a clinical response to therapy. Others have shown that a liquid biopsy can detect therapy resistance weeks or even months before standard of care imaging. It will be important to determine whether such early detection, especially when used to guide re-stratification of the patient onto a different therapy, has a positive effect on outcomes. Additionally, one of the most significant predictors of prognosis in NSCLC is the stage of disease at presentation, and our lab is actively focused on determining whether liquid biopsies can be utilized to identify patients with early stage disease.

Read this article on Real World Health Care.