Understanding the Polygenicity of Cancer

Researchers are using next-generation sequencing to predict cancer risk and tailor precision prevention.

Introduction

More than 18.1 million people worldwide received a cancer diagnosis in 2018, with more than 9.6 million individuals succumbing to the disease in the same timeframe.[1] The numbers are staggering and deciphering the genetics of cancer has become the focus of researchers worldwide. Beyond the small subset of cancers associated with strong single-gene traits, the difficulty is that many cancers are polygenic. Instead of being caused by a single "smoking gun" gene, many genetic loci are involved, with each contributing a small portion to cancer risk.[2] The challenge for clinicians is how to incorporate polygenic risk assessment and develop appropriate cancer screening and prevention methods, and prescribe targeted cancer therapies for treatment.

Jeffrey Weitzel, MD, has spent the last two decades attempting to understand the genomic causes of different forms of cancer and leverage that knowledge into screening and prevention. It's helped that he was one of the first oncologists in the United States to be also board-certified in genetics. As Chief of the Division of Clinical Cancer Genomics and Director of the Cancer Screening and Prevention Program at the City of Hope Comprehensive Center in Duarte, California, Dr. Weitzel is leading the charge to develop revolutionary new approaches to quantify cancer risk based on genomic information. The goal is to develop personalized cancer treatments, as well as personalized prevention plans.

iCommunity spoke with Dr. Weitzel about his aspirations for precision prevention, his work to expand genetic cancer screening in disadvantaged populations, the role next-generation sequencing (NGS) plays in his studies, and the importance of increasing human genetics education among researchers and clinicians internationally.

Q: What inspired you to specialize in oncology and cancer genomics?

Jeffrey Weitzel (JW): When I first started in oncology, we had chemotherapy, radiation, and surgery, but we didn't have genomics. We were looking at biomarkers, like receptors involved in breast cancer, but *HER2/neu* amplification was the closest we got to molecular work at the time.

When I began my hematology and oncology fellowship at Tufts University in 1987, inherited genes that predispose individuals to cancer, such as *TP53*, and Li Fraumeni syndrome, were just beginning to be identified. In 1990, *BRCA1* was identified and was the first gene established as a cause for breast and ovarian cancer. While I was at Tufts, they started a new fellowship in clinical genetics. I was an inaugural fellow as a full-time faculty member on a K08 grant. I then became board-certified in clinical genetics. At the time, that was kind of a unicorn qualification. It made me one of three people in the country who had boards in both oncology and genetics. It enabled me to pivot and focus my entire career on the genomic risks of cancer. I learned the power of genetics to tell us about predisposition for this disease.

Q: What is the focus of the programs that you oversee at City of Hope?

JW: Our programs are focused on understanding genomic risk and genomic biomarkers in a way that will enable us to tailor patient care. This includes targeted therapeutics and understanding a person's predisposition to cancer, what I refer to as precision prevention.

With precision prevention, we're identifying risk early so that we can monitor the person. For example, we start screening a *BRCA* mutation carrier at 25, not 40 years old. For someone with a *BRCA* mutation, 30-40% of cancers occur in the timeframe when they are 25-40 years old. Without precision prevention, we wouldn't know that they were at risk and would miss the opportunity to make an early diagnosis.

Our work in these programs entails everything from genetic epidemiology to targeted therapy development. Along that arc, NGS tools are enabling us to understand cancer risk and apply those tools to prevent cancer.

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Q: What prompted you to conduct studies on the genomic epidemiology of hereditary cancer, particularly in people of Hispanic ancestry?

JW: We are interested in studying genomic cancer risk in all people. One of the important aspects of genomic risk assessment is that we can change the course of disease in families.

The question for our team became, "Who doesn't have access to this type of assessment?" We became aware of significant disparity and established a pro bono clinic for underserved women at Olive View Hospital in north Los Angeles County. Eighty-nine percent of the population there are indigent, many are immigrants from Latin and South America. The oncologists at Olive View were providing care to young women who were presenting with Stage 3 breast cancer despite a family history of the disease, in part because of a lack of screening.

When we started, Medicaid wasn't paying for genetic tests. That's where our genomic innovation kicked in and we found cheaper ways to perform screening tests to bring down the costs and increase access. Along the way, we backed into the genomic epidemiology of breast cancer in Latinos. We went to Olive View to address a disparity and walked away with a knowledge base about the ontogeny of these mutations over thousands of years of history.

Q: What genetic analysis tools did you use initially for hereditary cancer research?

JW: We applied whatever tools were available. I wish I could say that I'm an innovator in developing tools. Instead, I've innovated ways to use the tools to make screening cheaper.

Initially, we used Sanger sequencing and I'm convinced I became nearsighted from reading sequencing gels. It was tedious, but it was informative and accurate. The first tests that were commercially available were expensive and insurance coverage was variable.

When NGS was introduced, there was a battle integrating sequencing into health care. After that battle was won, we could identify the individuals who were at risk. We spent the next decade figuring out how to help them.

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Q: How has NGS changed how genetic testing is performed in your studies?

JW: Early on, the cost of Sanger sequencing and time were a barrier. The original test turnaround time was three months. We thought it was amazing when we got that timeframe down to four weeks. With NGS, we can now analyze many genes simultaneously and obtain data in a week. It has allowed us to enrich our knowledge of genes beyond *BRCA*. While the *BRCA* genes are the two most important causal genes for breast cancer, we now understand there are another 20 or more genes involved, with at least five or six of them having clinical relevance. With NGS, the cost of sequencing 20, 34, or more genes is about the same. It doesn't make sense to sequence gene by gene anymore when we have a technology that delivers a clinically validated test of many genes for about $300.

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Yet, it's still not inexpensive enough for some economic settings. I'm trying to perform the same test at a sixth of the cost and even that is too expensive for some of the countries and cities where we provide a service, but it has enabled us to conduct more studies. We're now taking care of more than 3000 patients in Latin America, with the testing performed in my laboratory, and validation and care provided by the doctors who performed the risk assessments in their local communities.

Q: What have been the most significant contributions of NGS to hereditary cancer research?

JW: I think the biggest contribution has been the ability to do genomics quickly, at scale. But we are also discovering things about human biology now thanks to NGS that relate to things like clonal mosaicism. There is immense variation in the human genome among individuals. We start with one set of genes in one cell and, by the time the first cell division has occurred, there are already mistakes in the genome. Some of those accumulate over time. With the extreme sensitivity of NGS, we are learning about the underpinnings of genetic variation and the stochastic aspects that lead to cancer.

Q: What have you learned about the polygenicity of cancer?

JW: There have been many genome-wide association studies (GWAS) that have uncovered different single nucleotide polymorphisms (SNPs) associated with cancer. When we know the SNPs that are associated with a disease, we can start to calculate risk. Yet, the risk is minuscule for each SNP. There are almost no SNPs that confer tremendous risk. Most impart a risk less than two-fold, which isn't meaningful clinically.

Using the art of mathematical oncology and clever statistical geneticists, we can weight each SNP individually and combine multiple SNPs associated with breast cancer and come up with a polygenic score, or a mathematical assessment that allows you to calibrate risk across a range. Researchers have shown that they can stratify breast cancer risk in a non-*BRCA* population using 77

The research team at the Cancer Screening and Prevention Program at the City of Hope Comprehensive Center in Duarte, California.

biomarkers, with women at the high end at 30% risk and at the low end with 5% risk.[3] We could split that risk out using a polygenic risk score. That's very exciting work.

The next step will be our ability to predict breast cancer risk in people who have moderate risk variants like *CHEK2* or *ATM* genes, where the risk is between 20-35%. We'll be able to take the polygenic risk score and superimpose it over the genetic basis to show that a moderate risk gene can become a high-risk gene in certain individuals because of their SNP profile.

Q: What could the value of polygenic risk scores be in cancer diagnosis and treatment decisions?
JW: These scores are a work in progress and have not been clinically validated for treatment. However, one day we could use them to calibrate the risk of cancer interventions. For example, a polygenic score could inform a clinician that the presence of a moderate risk gene doesn't warrant surgical risk reduction. We've always had high-, moderate-, or low-risk cases. With polygenic risk scores, we're starting to fill in the gaps between them.

The science of how we interpret these risk scores and how they are applied in the clinic will help us with the translation and integration. We are at the cusp of this research and are reaching the point of application in the clinical setting to see how it might influence care and assist clinicians and patients in deciding whether to perform risk reduction surgery or to continue regular surveillance.

Q: Does the ability of NGS to identify many more variants present analysis problems?
JW: The problem isn't the technology, it's the skill of the people interpreting the results of the technology. In genetics and genomics, the technology has always been ahead of our understanding. We identify a gene and conduct the testing before we know what the data means and what to do with it.

However, NGS is leading us in a good direction. It is increasing the accessibility of screening, and the ability to sequence tumors and the germline of individuals. That's why we perform cascade testing. When we find something that has a causal effect and increases a person's risk for cancer, we're using genetic tests to identify those at risk and try to do something to help prevent disease. That's precision prevention.

I predict, in the next five years, the most comprehensive cancer centers will be sequencing everyone's tumors and every germline as they come in the door to better understand the underpinnings of cancer.

Q: What's your vision for the future of genetic risk assessment?
JW: In many advanced economies, countries can deploy fairly sophisticated testing and are already performing general population screenings. However, in other countries there are whole population segments who are unable to access what we consider medically necessary care. These global disparities in health care need to be addressed – prevention is always better than cure. Given economies inherent in NGS, low and middle income countries can embrace prevention if they can establish the trained workforce needed for implementation and public health finance to sustain the process.

We also need to expand our understanding of cancer and what we can do to get to precision prevention. I think we're getting more precise about our risk assessment. We're moving into polygenic risk scores, which provide an intelligent way to stratify the risks of developing cancer. We're also learning more about the modifiers of that risk so we can personalize care. My vision is that we get to the point where we're able to apply these tools in an economical way across the whole population, anticipate the risk, and provide the necessary care before someone gets cancer and, if possible, prevent it altogether.

Q: Together with Kathleen Blazer, EDD, MS, LCGC, you recently received the 2019 American Society of Human Genetics (ASHG) Arno Motulsky-Barton Childs award for human genetics education. How will medical education be important to achieving your vision?

JW: We were extraordinarily proud to receive the award. As a team, we have deployed an intense training focused on cancer and genetics. It's taken us a couple of decades to develop these programs. When I started to learn genetics, I did it the hard way and earned a degree in it. In the USA, a clinician doesn't have to have a genomics background to order a genetic test. However, there is a knowledge gap of what the results mean and how they should be applied. Our goal is to raise the genomic competency and understanding of community clinicians to the level of expertise found in academic health centers. No one can do this work on an island and the field is changing rapidly. Clinicians need to be connected to an active learning environment where they can learn within the context of how it applies to their work.

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We are always going to need professional educators in this area because the technology and our knowledge base changes so quickly. We've worked hard to create dynamic curricula that can adapt to this rapidly changing landscape. We need to have more adaptive ways of teaching so we can get clinicians the bolus of learning that brings them up to speed, as well as a supportive learning community that can help them stay up to date. We plan to continue scaling up the program to reach more health care professionals and move the bar in terms of quality of cancer care in community settings here and throughout the world.

To learn more about integrating genetics into cancer care, visit www.cityofhope.org/ic.

Learn more about the products and systems mentioned in this article:

TruSight Hereditary Cancer Panel,
www.illumina.com/TruSightHereditaryCancer

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