



GENOMICS AND THE FUTURE OF CANCER TREATMENT

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Centuries ago, when disease was thought to result from a disruption of the body's four basic "humors" – fluids that collectively governed health – treatments were designed to bring them back into balance. "Therapies," some of them ghastly by modern standards, were intended to relieve patients of harmful surpluses of certain humors.

Thankfully, medicine has advanced far beyond that era. However, it's clear that how we understand or conceptualize a disease affects how we treat it. Those who will look back on our efforts decades from now may marvel at the limitations of our knowledge about the true nature of the diseases we sought to conquer.

Consider cancer. For more than a century, cancers have been classified by the organ or tissue where they begin – the breast, lungs, bone marrow, digestive system, and so on – and therapies have been geared to those specific areas. Fortunately, as we've learned more about the basic biological processes at work in cancer, a new perspective has emerged. Soon, we may regard the organ-based conceptions as being as outmoded as the "humors."

Increasingly, we're able to study cancer not only at the most fundamental, molecular level but also at the level of interacting systems and networks. We have gained crucial insights, for example, into how the immune system fights cancer and why that fight isn't always successful. We've learned how tumors tap into the body's bloodstream for nourishment and how those supply lines can potentially be shut off. We've learned how tumors communicate with healthy, surrounding tissue, and how that neighboring tissue sometimes abets the cancer process.

The best known of these advances in "systems" biology, perhaps, is genomics, which provides a "snapshot" of gene activity within a cell. As our knowledge grows, there has been a shift away from viewing cancer in terms of the organ where a tumor forms, and toward a concern with the genetic instructions that govern both the growth and division of individual tumor cells and the interaction of the tumor with the person who serves as its unwilling host.

To carry this work forward, we need a far more collaborative approach to research, with

an emphasis on rapidly converting basic scientific insights into practical treatments that work in patients. By creating “Dream Teams” of scientists and specialists from different disciplines, Stand Up To Cancer is mobilizing precisely this kind of effort. It is one reason why the program holds so much promise for turning the tide against cancer.

The trend toward a genomic approach to cancer is gaining momentum every day. Research has shown, for example, that certain lung cancers have some of the same abnormal, or mutated, genes as some brain cancers. Gene mutations that sometimes show up in breast and ovarian cancers also occasionally appear in prostate cancers. Such similarities may turn out to be far more significant, from a treatment standpoint, than the fact that the tumors arose in different organs. A striking example of this occurred earlier this year. A patient with metastatic melanoma – an often fatal cancer that begins in the skin – came to [Dana-Farber Cancer Institute](#) in Boston, for treatment. Genetic tests showed that her tumors harbored a mutated gene called KIT, which is often found in patients with chronic myelogenous leukemia (CML). Her doctors treated her with the drug Gleevec, which was originally designed for CML patients with mutations in KIT. The result: her cancer went into complete remission – the first time that has ever been accomplished in metastatic melanoma. She and an increasing number of others like her provide another lesson: every person’s tumor is unique. That is why the goal of “personalized medicine” is so compelling.

Cancer has always been known as an illness of many guises. When we talk about cancer today, we’re actually referring to a family of diseases – more than 400 in all – characterized by the uncontrolled growth and spread of abnormal cells. As we begin to identify cancers by their genetic “signatures” – the specific set of mutated genes within their DNA – it may turn out that there are even more types and subtypes than we currently recognize.

The shift from an organ-focused to a gene-focused approach to cancer is already having a profound effect on the way cancer is treated. The impact can be seen particularly clearly in breast cancer. Not too many years ago, breast tumors were categorized and treated primarily by their size, the degree to which they had invaded surrounding tissue or sloughed off cells into the lymph system, and their appearance under a pathologist’s microscope.

Today, breast tumor tissue is routinely analyzed to determine if it is “ER positive,” meaning its growth is fueled by the hormone estrogen, and if it has an abnormality in the gene HER-2/neu. Patients whose tumors are ER positive can be treated with antiestrogen agents, and those with an HER-2/neu mutation may receive the drug Herceptin, which targets the malfunctioning gene. Genetic testing also enables doctors to identify women with inherited mutations in the genes BRCA1 and BRCA2, which increases people’s risk of breast and other cancers. Although no easy preventive treatment yet exists for those with BRCA mutations, women who test positive for them can take steps to ensure new tumors are caught as quickly as possible.

Together, these advances mean that about 85 percent of all breast cancers can now be

distinguished as ER-positive or having BRCA or HER-2/neu mutations, or some combination of the three – and be treated accordingly.

This ability to match therapies to breast tumors' genetic vulnerabilities is a preview of what we hope to be able to accomplish for all cancers. Such "targeted" therapies have already had an enormous impact for three other groups of patients – those with chronic myelogenous leukemia, those with a rare digestive-tract cancer called gastrointestinal stromal tumor, or GIST, and the roughly 12 percent of lung cancer patients whose tumors have a defect in the gene EGFR. In all three cases, targeted therapies routinely produce remissions in patients who otherwise would have no effective options for treatment.

The capacity to "type" tumors by their genetic profiles will have other benefits as well. In prostate cancer, for example, we currently don't know which tumors are likely to spread – and therefore require urgent treatment – and which are likely to be so slow-growing they'll never pose a health threat. As a result, we tend to treat all prostate cancers as if they're of the most ferocious variety. By understanding which genes brand a tumor as especially aggressive, we'll be able to provide not only the right treatment, but the right degree of treatment, and at the right time.

The impact of these and other advances can be seen in increasing survival rates for a variety of cancers. Thirty years ago, the five-year survival rate for cancers in general was less than 50 percent. Today, it is higher than 66 percent.

For all its promise, the field of cancer genomics is less than a decade old. The progress in mapping out cancer's genetic variety, though substantial, is still at a relatively early stage. As we fill in the map and develop a new taxonomy for cancer – a new system for distinguishing tumor types and subtypes – the advances promise to be enormous. But we are still learning how to use these powerful new tools. Much remains to be done.

Nonetheless, the opportunity for a decisive push against cancer has never been more assured – and this is why support from the Stand Up To Cancer campaign is so crucial. By encouraging collaboration between eminent, established researchers and talented young scientists and by bringing people from many scientific fields together, the campaign encourages precisely the melding of innovation and experience, depth and breadth that is vital for continued progress. The elements of future breakthroughs are steadily coming into sight; we can be the generation that puts them together to finally break the back of cancer.

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