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EDITORIAL – BREAST ONCOLOGY

Genetics, Genomics, and Pharmacogenomics

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A better understanding of the genetic basis of disease has led to new opportunities for preventing and treating cancer under the rubric of personalized medicine. However, this development has been accompanied by an order of magnitude increase in information to process at a level likely beyond what the unaided mind of the physician can manage.

Although this series concentrates on the genomic basis of cancer staging and treatment, it is useful to step back and understand some of the terms that have begun to define modern genetic medicine. Physicians will need not only to understand these terms but also to put these concepts to work in their daily practice of medicine. The following is likely an oversimplification, but it offers some context as to how we will be practicing medicine for the foreseeable future.

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Let's think first about germ-line versus somatic DNA. Germ-line DNA is inherited at birth from each parent, while somatic DNA is the current state of that DNA in each cell of the body. Somatic DNA is relatively stable, and each cell has a fairly complete and accurate copy of the germ-line DNA that they inherited at birth. However, some cells, over time, can develop mutations in their somatic DNA (i.e., develop somatic mutations). Cancer is essentially a collection of a set of mutations in a single cell that cause the cell to no longer follow the rules of engagement with its fellow cells, causing it to grow uncontrollably and to metastasize.

GENETICS

The term genetics is sometimes used to refer to the state of the germ-line DNA (before any somatic mutations). Germ-line DNA mutations, such as *BRCA1* mutations, are passed from parent to child and are found in the somatic DNA of every cell in the body. It is of interest that although these mutations occur in every cell, they seem to selectively cause cancer in only a few cell types. For example, a *BRCA1* mutation in every breast cell only causes cancer in a subset of these cells, whereas a *BRCA1* mutation in every liver cell does not cause an increased risk of liver cancer. The increase in breast cancer development appears to be the result of the mutation causing the loss of *BRCA1*'s tumor suppressor function.[1] Although each breast cell has 1 mutated *BRCA1* from 1 parent, it also has a normal *BRCA1* gene from the other parent. Cancer development likely requires loss of the normal *BRCA1* gene, so that the individual cell now has no normally functioning *BRCA1* protein. On the basis of Knudson's 2-hit hypothesis, cancer development requires the loss of both tumor suppressor genes, which explains the earlier onset of disease and the more frequent incidence of these diseases in women carrying these mutations (i.e., those born with one hit already).

Once the normal *BRCA1* is lost (the second hit), further mutations accumulate rapidly (as the *BRCA1* protein's DNA guardian function has been compromised), and cancer develops.[2] As a further complication, the possibility of a dose effect has been raised, suggesting that even when the normal *BRCA1* is still functioning, it may not produce enough protein to protect the genome.[3]

PHARMACOGENOMICS

Pharmacogenomics is an extension of germ-line genetics in a different direction. It usually refers to patient response to drugs in relation to their genetic makeup. Many drugs must be either metabolized to their active metabolite in order to be effective or deactivated to nonfunctioning metabolites in order to avoid toxicity. The germ-line DNA present in certain cells effects the metabolism of certain drugs, regulating either the amount of effective metabolites produced or the speed at which toxic molecules are degraded. This might increase the amount of active metabolites, causing the same dose of drug to be more effective or more toxic in certain patients. On the other hand, the decreased ability to metabolize a drug to its active metabolite could cause the drug to be less effective.

The following are some examples of drugs that display the importance of pharmacogenomics in clinical practice.

Warfarin (Coumadin)

Warfarin has been the standard treatment for oral anticoagulant therapy for many years. However, it is also well known for its narrow therapeutic index with varying pharmacologic responses among individuals, and thus it requires frequent monitoring with the international normalized ratio. This variation is one of the leading causes of hospitalization from adverse drug events.[4,5] Numerous retrospective studies have found that the variations in the enzyme responsible for metabolizing warfarin, CYP2C9, and the gene that encodes the drug's target, *VKORC1,* are strongly associated with lower warfarin dose requirement.[6–9] Patients in these subgroups will therefore have difficulty at induction of warfarin therapy, as they metabolize it at a slower rate than those with the wild-type alleles. The warfarin levels of these patients will fall slowly, which can potentially lead to a higher risk of bleeding complications. Through the use of pharmacogenomic approaches (e.g., identifying the genetic makeup of the individual to determine dose), it may be possible to reduce adverse drug reactions by tailoring the dosage to each patient's ability to metabolize the drug.

5-Fluorouracil

5-Fluorouracil (5-FU) has been a major drug for almost 50 years in the treatment of solid malignancies, especially in colorectal cancer.[10] The drug's active metabolite targets an important enzyme in cell proliferation, thymidylate synthase. Like many antitumor agents, 5-FU's dose must be calibrated carefully between tumor response and toxicity. A higher dose can result in severe toxic adverse effects, including death (0.1 %) as a result of catabolic pathway deficiency.[11–14] Dihydropyrimidine dehydrogenase (DPYD) is the key enzyme of concern, and with the help of pharmacogenomics, physicians can detect the degree of DPYD deficiency and discover the best-tolerated and most effective dose, as well as potentially prevent severe toxicity.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator, and it is an essential drug used for the prevention and treatment of hormone receptor–positive breast cancer. Early studies have shown an approximately 40 % reduction in recurrence rates and a 30 % reduction in mortality rates with the use of this drug.[15] Thus, many medical societies recommend that all women with hormone receptor–positive breast cancer receive Tamoxifen for 5 years, and the American Society of Clinical Oncology recommends treatment for 10 years for prevention of recurrence.[16] The antiestrogenic effects of tamoxifen comes from its active metabolite, endoxifen, and the key enzyme that mediates this conversion is the highly polymorphic CYP2D6.[17,18] Those with the certain variants of CYP2D6 showed a significant difference in disease outcome.[19,20] In order to exceed the threshold endoxifen concentration, physicians may identify the CYP2D6 genotype and adjust the dosing accordingly to yield the optimal result.

GENOMICS

Genomics typically refers to the somatic mutations accumulated by a cancer. This is the focus of the articles in this series. Cancer is the accumulation of somatic mutations. Some of these mutations will increase growth rate, while others tend to decrease the ability of the cell to repair DNA, hastening the collection of further mutations. In breast cancer, it has become common practice to analyze DNA signatures of tumors to help determine the best course of treatment and the prognosis. It has been found that that certain DNA signatures are related to a faster growth rate of that cancer. It has also been found that those cancers with faster growth rates tend to identify patients who benefit more from chemotherapy. Although this relationship to chemotherapy efficacy might have been expected,

it was not a foregone conclusion. In addition, the presence of certain somatic mutations increases or decreases the utility of certain drugs.

As a further addition to the complexity, some germ-line mutations in cancer susceptibility genes affect which drug is the best to use for cancers that develop. For example, cancers in *BRCA1* mutation carriers might be more responsive to platinum or Poly ADP ribose polymerase (PARP) inhibitor therapy.[21,22]

SUMMARY

The message is clear. Molecular biology will inform our approach to cancer treatment, whether we consider this genetics, genomics, or pharmacogenomics. The following articles describe the beginnings of a conceptual framework for the effect of genomics in managing cancer of 4 major organs. We are moving to an era where the screening, prevention, and treatment of cancer will be selected specifically for the individual patient on the basis of their genetic makeup and the genetic makeup of their cancer, with the goal of increasing efficacy, decreasing toxicity, and avoiding treatments unlikely to be effective.

As we move into this era, we will become more and more dependent on clinical decision support (CDS), the use of computer algorithms for identifying the best course of action.[23] At this point, CDS is being done for us in a rudimentary way by the testing labs. A gene signature is scored as high risk by a computer, and we are told the patent's score is high as part of the laboratory report. Currently we decide treatment by collating the lab report with other factors using our unaided minds. As genetic and pharmacogenomics information become available, CDS will be needed to help patients and physicians integrate this massive amount of data into an accepted course of therapy.

To incorporate pharmacogenomics considerations in the treatment recommendation, a physician will be given the germ-line DNA sequence with some suggestions about which drugs may be effective or ineffective and which drugs may be toxic or nontoxic and with suggested dosing. To incorporate the genetic consideration, the physician will also have the germ-line DNA sequence relative to major or minor genes that cause cancer susceptibility and also, as in *BRCA1*'s case, suggest which drug to use. And to incorporate the genomic consideration, the physician will have the genomic makeup of the cancer, with stated information about high versus low risk and the efficacy of chemotherapy or other treatments. The ultimate challenge is for the treating physician to synthesize this information and integrate it with the age and health status of the patient, the stage of the cancer, and any prior therapies to tailor the treatment recommendation to the individual patient.

The future is unfolding rapidly, and we are being confronted with almost limitless information. Unfortunately, the human mind is limited in what it can comprehend and synthesize. The massive power of genetics, pharmacogenomics, and genomics will depend on shifting away from memory-based medicine and toward CDS.[24,25] In the interim, we will need to carry on as best we can. In some ways, medicine today is analogous to a jumbo jet pilot who is forced to use a slide rule and a sextant to navigate. The genetics, genomics, and pharmacogenomics era will force us to move rapidly into the computer age. We can only hope that health information technology can keep up.

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