Is it possible that our quality of life (QOL) is influenced by genetics? This novel question has recently been undertaken by the North Central Cancer Treatment by exploring the linkage between a cancer patient’s QOL and the person’s genetic makeup. The theoretical framework for the concept is based on the premise that human endeavor is a combination of biological and environmental factors. By way of an analogy, the QOL of a plant, or the degree to which it thrives, is a function of the seed from which it sprung, the soil in which it is planted, and the amount of sunlight it enjoys. Similarly, the QOL of humans can be described as a function of the genetic seed, the soil of situational characteristics, and the sunshine experienced through life events.

Many cancer studies link genetics and treatment outcomes, which then links treatment and QOL outcomes, but not directly between genetics and QOL outcomes. The following quote exemplifies the typical manner in which genetics and QOL have been related in the oncology literature: “Through an understanding of the molecular processes that occur in the development and progression of prostate cancer, novel therapies will arise that will provide longer survival, better quality of life, and a chance for cure.”

Because the genes affect basic cell processes, they may affect how a patient feels overall. It is possible that a patient’s genetic make-up may contribute not only to specific chemotherapeutic agents, but also may influence the individual patient’s QOL during treatment. We know that cancer patients who have good QOL and do not feel tired all the time or stressed out tend to cope better with the burden of having cancer.

Genetic Predispositions for Psychological Variables

Bouchard and Loehlin argued that much social science research is seriously compromised if it does not incorporate genetic variation in its exploratory models. There is abundant empirical evidence that virtually all human psychological traits are influenced by genetic factors to a
significant degree. A great deal has been learned about the role of genetic influences on personality in recent years.

Recent research has suggested a genetic predisposition for depression, suicide, alcoholism, smoking, aggression, resilience, and other psychological parameters. The genetic aspect of diseases other than cancer has resulted in, among other things, the identification of the so-called Alzheimer’s gene. The epsilon4 allele of the APOE gene has been investigated for association with health-related outcomes in the elderly and related to cognitive changes in patients with Alzheimer’s. Other genes involved include the 5-HT receptor, and androgen-regulator genes. For example, in a study published of 490 subjects, Huang in 2003 identified differences in 5-HT receptor frequencies between those with psychiatric disorders related to alcoholism, mood, suicide, and aggression and normal volunteers. Similarly, in 1998, Lappalainen reported findings that antisocial alcoholics were more likely to have the 861c allele, indicating a genetic foundation for alcoholism. Other translational cancer research has explored the genetic basis for response to treatment and patient survival. But the degree to which genetic structure impacts biologic activity and psychosocial response to a cancer diagnosis is still unknown.

Genetic studies on twins form the largest body of research of genetic variables. Studies on twins have been a core method to explore the extent to which genetics and the environment influence human behavior. Variation in religiousness is moderately influenced by genetic factors. The Minnesota Study of Twins Reared Apart has led to two general and seemingly remarkable conclusions concerning the sources of human psychological differences: (1) genetic factors exert a pronounced and pervasive influence on behavioral variability, and (2) the effect of being reared in the same home is negligible for many psychological traits. Studies of genes coding for proteins involving serotonergic neurotransmission indicate that genetic factors are a risk factor for suicidal behavior. There is recent evidence that polymorphisms impact responses to psychosocial stress. Baghei recently published a study wherein gene polymorphisms genes regulating androgen were associated with personality traits among women. Indeed, a twins study published last year in the UK which suggested genetic heritability of psychosocial distress may account for as much as 44% of the total variability. The measure involved, the General Health Questionnaire, is not that different from a measure of QOL.
Genetics and Cancer-Related QOL

It is not a giant leap of faith then to expect that there should be a relationship between an individual’s genetic makeup and the manner in which an individual reacts to the stress of a cancer diagnosis or the trajectory that the individual tracks through the disease process. On an intuitive level, one may say there is reason to suggest a genetic background to why some people are simply more energetic and enjoy a better QOL in the same way that there are genetic predispositions for physical attributes such as height or eye color.

There has even been some preliminary evidence of a genetic role in an individual’s well-being. A study by Romeis published 6 years ago investigated the heritability of self-reported health by employing a large twins database of over 4600 people from the Vietnam Era Twin Registry. Romeis tapped this database for a series of multiple regression models using a 5-point self assessment of health as the dependent variable. Results of this modeling procedure indicated that genetic variables selected from the registry database accounted for as much as a third of the variability in self-reported health.

Further preliminary evidence suggests that a cancer patient’s genetic makeup influences how the patient experiences fatigue, one of the most common side effects of cancer. It is believed to be the first finding of a possible link between genetics and a cancer patient’s QOL. The North Central Cancer Treatment Group recently completed a hypothesis-generating study which aimed to investigate the existence of a direct link between genetic variation and cancer patient QOL, independent of cancer treatment and outcomes. More precisely, it was hypothesized that variations in specific genes will correlate with cancer patient QOL before any chemotherapy is given. The hypothesis was tested as part of a large-scale phase III NCCTG clinical trial of patients with colorectal cancer in which both QOL variables and genetic markers were included. Sufficient evidence was found to suggest that there may be a link between genetic structure and QOL. Specifically, there may be genetically related cellular functions that impact cancer patients’ QOL.

We evaluated 494 patients with advanced colorectal cancer being treated with new chemotherapy regimen 5-fluorouracil, irinotecan, and oxaliplatin. Common side effects of this therapy include fatigue, nausea, vomiting, diarrhea, low white blood-cell counts, dehydration, and numbness in the hands and feet. Three specific folate genes were examined—DPYD, MTHFR, and TYMS—which are a critical gauge of cellular
health. These genetic variants have been present for much longer than the chemotherapy agents involved in this study. Therefore, it is reasonable to assume that these genes serve other cellular functions. Seven of the genes have known functions with respect to the broad category that we refer to here as cellular health. They have functions in neurotransmitter synthesis, serve as methyl donors, play a role in DNA synthesis or damage repair, or detoxify the cell. Many of these functions mediate the cell’s response to stress. It therefore seems reasonable to postulate that they may have some effect in their control of cellular function in the organism’s response to a disease such as cancer.

The primary finding is indicated in Figure 1, relationship between DPYD_5 and patient-reported fatigue at baseline. Both a statistically and clinically significant difference, of more than 10 points in average fatigue, was observed between normal and variant genotypes. Specifically, the A/A genotype or homozygous variant was associated with lower fatigue scores, indicating worse QOL.

Seven different markers indicated a relationship with patient-reported fatigue. In total, more than triple the number of relationships were observed than one would expect by chance alone between QOL and genetic variables.

![Differences in Mean Fatigue Scores for 20 Genetic Markers Between Patients With Normal vs Wild Type Variants](image)

**FIG 1.** Differences in mean fatigue scores for genetic markers between normal and variant genotypes.
Future Investigation

In this exploratory study, we looked at only a few markers and specifically targeted QOL endpoints related to colorectal cancer. We are continuing to explore this research hypothesis involving other candidate genes that we believe may be related specifically to the cancer diagnosis and etiology. Recall that in our study the genes were not specifically chosen for a relationship with QOL, but instead with the treatments involved in the clinical trial. We believe there are other more specific markers that will link directly to the disease itself. Prospective studies are being designed for this purpose. Clearly, the path forward is complex and multivariate in nature, considering the potential number of genes and QOL variables that may be involved.

This study opens the door to explore new pathways of improving patient care. Certainly, over the last 10 years, progress in basic cell science has outpaced its clinical utilization, and new collaborations with seamless integration of disparate disciplines must occur to successfully explore these new concepts. Future studies will need to further examine the genes identified in this study to validate these findings as well as to identify other potential genetic markers. The ultimate goal would be to use information about a cancer patient’s genetic makeup to tailor individualized treatments for QOL in the same manner as individualized treatments for the tumor itself. Doctors will eventually use genetic patterns for several tasks: to tell whether a cancer will spread, to predict how various therapies such as specific drugs or radiation will work, and perhaps even to see how someone’s QOL will be affected.

REFERENCES

6. Horwitz AV, Videon TM, Schmitz MF, Davis D. Rethinking twins and