DIAGNOSIS: THE BUCK STARTS HERE

THE ROLE OF DIAGNOSIS IN THREE AREAS OF MODERN MEDICINE

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ABSTRACT

PRASHANT NAIR: Diagnosis: The buck starts here. The role of diagnosis in three areas of modern medicine

(Under the direction of Tom Linden, Jan Yopp and Nortin Hadler)

This thesis examines the role of diagnosis—traditional and molecular—in three areas of medicine: personalized cancer treatment, treatment of infectious diseases and treatment of controversial disorders lacking unambiguous physiological bases. The thesis uses a mix of statistics, expert interviews and patient anecdotes to address in the form of three feature stories three aspects pertinent to the role of diagnosis in modern medicine. The first story addresses the challenges to developing diagnostic markers for truly personalized cancer therapy. The second story features a recent advance in molecular diagnostics that has transformed the treatment of infectious diseases, especially hitherto-unknown viral infections. The third story illustrates the plight of patients suffering from disorders whose very existence is controversial and for which doctors are unable to provide clear-cut diagnoses.

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CHAPTER I

INTRODUCTION

The past decade of innovation in molecular biology has ushered in a new era of medicine. Personalized medicine, or the approach of fashioning treatments and prevention strategies for individuals and their diseases, is slowly changing the treatment of a range of disorders. Dr. Francis Collins, the former head of the Human Genome Project, defined personalized medicine as "using information about a person's genetic makeup to tailor strategies for the detection, treatment or prevention of disease." While this new movement in medicine has been afoot, advance is glacial, largely because of the enormous biological variability among individuals. To be successful, personalized medicine depends on an array of scientific disciplines and on collaboration between basic researchers and clinicians. In large measure, personalized medicine hinges on accurate diagnosis. Information about a specific individual or groups of individuals who share similar genetic or physiological characteristics helps doctors tailor treatment to groups of patients. Characterizing the patient's ailment as comprehensively as the existing technology allows is the first step in developing designer drugs for personalized therapy and elevates diagnosis to a central role in personalized medicine. Indeed, physicians practicing personalized medicine must consider the corollary question that tries to define individual variability: *Is one person's heart attack or prostate cancer biologically different from another's for a reason not based entirely on chance?*

To be sure, personalized medicine is in its infancy; the real deal—individualized therapy—is pie in the sky, largely because many diseases are minimally heritable and also because many diseases are controlled by multiple genetic factors. But the development of new diagnostic procedures, the mapping of the human genome and technological strides in biology have kick-started the march of personalized therapy into mainstream medicine. Nowhere is this more striking than in the arenas of cancer therapy.

The trend in cancer therapy has been to move away from the traditional paradigm of treating tumors based on where in the body they originate to targeting them based on their genetic signatures and on the panoply of biochemical pathways that drive their reckless growth and spread. In a nod to personalized medicine, researchers are working toward cataloguing the plethora of mutations in the cancer genome. This multinational effort, called the International Cancer Genome Consortium, is aimed at documenting all possible mutations in 50 of the most common cancers by sequencing DNA from a minimum of 25,000 individual tumors.

Diagnostic tools to illuminate the genetics of cancer have not only started to reshape patient care but have also influenced the development of novel, effective treatment options for patients. The goal of molecular diagnosis is to transform cancer from a death sentence into a manageable chronic condition. Starting with the 1960 discovery of the genetic aberration called the Philadelphia chromosome in patients suffering from Chronic Myeloid Leukemia (CML), researchers have discovered a number of oncogenes and tumor-suppressor genes whose mutant forms trigger different types of cancer. That, in turn, has led to a handful of targeted drugs, like Gleevec and Tarceva,

which slam the brakes on runaway cell division in specific patient groups. Since 2001, more than 30 new cancer treatments have been approved by the U.S. Food and Drug Administration (FDA). Some of those are based on the molecular characteristics of individual tumors.

For example, Novartis' Gleevec, the poster-child cancer drug known by the generic name imatinib mesylate, inhibits an enzyme—tyrosine kinase—whose activity causes uncontrolled cell proliferation and CML in patients harboring a mutation in the gene implicated in that cancer. In some CML patients, however, Gleevec fails to work after a while because of the onset of additional mutations in the gene that render the enzyme resistant to the drug. For these patients, Bristol Myer Squibb's cancer drug dasatinib was found to be effective against the majority of mutations conferring resistance to Gleevec, according an article published in 2004 in the journal *Science*.

To develop such precisely targeted treatments for cancer, scientists require markers that would predict a patient's response to therapy, the potential toxicity related to the treatment and prognosis. A small number of such markers guide cancer treatment in the clinic today. Indeed, they may be seen as a sort of barcode that's used to distinguish one tumor from another, for example, a piece of cancerous brain from a nub of breast tumor. These markers are important to cancer care but their reliability and validity are debatable.

On another front, diagnostic tools have transformed the treatment of infectious diseases. Timely and accurate diagnosis is essential to treating patients infected with little-known or hitherto unknown pathogens and for curbing the spread of infectious

diseases, thus serving an important public health function. Novel diagnostic tools for clinical use must be approved by the FDA. The agency discriminates between two types of diagnostics based on the analysis of DNA, or its chemical relative RNA: *genetic diagnostics,* which determines the presence or absence of a particular targeted DNA sequence already known to be related to a health outcome, and *genomic diagnostics* which measures gene expression, a term scientists use to describe gene activity, such as the production of proteins implicated in disease.

The technology to develop diagnostics for infectious diseases is available, but it has not been widely applied to the diagnosis or detection of emerging infectious diseases. Emerging infections are new diseases that are constantly appearing in populations, such as Severe Acute Respiratory Syndrome, West Nile virus infection, drug-resistant forms of tuberculosis and tropical diseases like malaria. Standard diagnostic procedures for these neglected diseases are weak and unreliable, such as sputum microscopy, skin testing, and radiography for tuberculosis, and some are notoriously difficult to carry out, such as the microscopic techniques used to diagnose malaria. Microscopic diagnosis of malaria is subject to a great deal of variability that depends on the accuracy of the investigator.

One promising diagnostic tool in the arsenal of infectious diseases specialists is called the *microarray* or gene chip. A gene chip is a short stretch of genetic material—DNA or RNA—immobilized on a solid surface, such as a glass slide or a wafer of silicon. Chips are sensitive enough to detect subtle differences in the identity of pathogens that are much harder to spot with other molecular methods. Scientists use gene chips to detect the presence of disease-causing organisms in patients' genetic material by matching the

genetic sequences on the chip with those found in the patients' samples. The unraveling of the genomes of many pathogens has allowed scientists to design chips to detect novel infectious disease agents. Further, chips allow the simultaneous detection and analysis of thousands of snippets of genetic material in a single experiment.

A particularly promising use of chips has been in the detection of viral diseases using the Virus Chip, developed by a young Californian researcher who helped the Centers for Disease Control and Prevention confirm the identity of a virus that wreaked havoc in large swaths of Southeast Asia. The Virus Chip helped determine that the virus that caused Severe Acute Respiratory Syndrome (SARS) was a novel member of the family of coronaviruses. Now, the chip's designer is using the technology to help diagnose emerging infections. He is participating in the launch of a new center for the diagnosis and detection of hitherto unidentified pathogens. He hopes to make the new center available for routine clinical diagnosis and for the ongoing battle against emerging infections. But the chip's story is also a cautionary tale about the challenges to the widespread adoption of microarray technology in the clinic.

For people with mysterious illnesses whose pathology—and indicators of pathology—are elusive, the road to recovery is often long and tiresome. Buffeted by doubt, anxiety and a range of baffling symptoms, these patients are forever in a quest for a name for their condition. Many such conditions that have names are mired in controversy. Fibromyalgia, chronic fatigue syndrome and chronic Lyme disease are a few examples. While some physicians are convinced of the existence of elusive pathophysiological causes for these disorders, others argue that these conditions must be

treated with little or no medication. The U.S. National Institutes of Health (NIH) launched a new center in May 2008 to bring together a team of 25 physicians and scientists from the NIH Clinical Center and the National Human Genome Research Institute to address these questions under the umbrella of the *Undiagnosed Diseases* Program.

Justification of Study

While the mainstream media have touted personalized medicine as the wave of the future, many stories present the promise of personalized medicine using anecdotal victories without explaining the challenges to the success of the approach. Little more than short shrift has been paid to the role of molecular diagnosis in personalized medicine. As the articles listed in the bibliography of this thesis attest, *The New York Times*, *The Washington Post*, *Newsday*, *New Scientist*, *Discover*, *Scientific American* and *The Scientist* have covered personalized cancer treatment extensively, but the vast majority of the coverage has presented the promise of personalized medicine without commensurately exploring the shortcomings and the challenges to the approach. Some of these stories bear sensational headlines such as "A special drug just for you, at the end of a long pipeline," "A drug to call one's own," and "Saving lives with tailor-made medication." While the overall message these stories convey—that cancer treatment is moving away from an organ-centered approach to a patient-centered one—is powerful, tempering the message's implicit optimism by laying out the caveats to personalized medicine is equally important. More importantly, few stories mention that personalized

medicine may not be a concept ready for prime-time. In that sense, these stories leave much to be desired.

The role of novel diagnostics in treating infectious diseases, in identifying novel pathogens, and in curbing the spread of emerging infections is little known to lay audiences. A review of the mainstream media revealed fewer than a half-dozen news stories that discussed the role of chips in the diagnosis of infectious diseases in clinical and in epidemiological settings. Local media in the San Francisco Bay area, including *The San Francisco Chronicle*, *The Sacramento Bee* and *The San Francisco Business Times*, have covered the use of microarrays in infectious diseases, partly because of the proximity of these media outlets to the laboratory of Joseph DeRisi, who received recognition for his discovery of the Virus Chip. *The New York Times* did a short Q&A with DeRisi on the tool's promise and on his future plans. But there haven't been many news stories in the media that explain how microarrays could transform the diagnosis of mysterious infections; trade journals such as *The Scientist* and *Science* have explored the topic briefly. Fewer still are stories that explain the promise of microarrays as frontline screening tools that could help doctors rule out a large number of disease-causing organisms when faced with a sample from a patient suffering a condition of baffling but likely infectious origin. Journalists have seemingly shied away from some of those stories because of the complexity of medical language used in research. But medical breakthroughs and treatment should be covered and translated in a way that makes sense to average citizens and makes information useful to them in seeking diagnosis and treatment of disease.

Much needs to be covered within the broad subject of diagnosis in modern medicine. While the topics are many, this thesis will consider three aspects: developing research, direct application of knowledge and remaining questions. The thesis, a series of three articles, specifically explains the diagnostic challenges to personalized cancer therapy, the role of cutting-edge diagnosis in treating infectious diseases and the controversy surrounding the diagnosis of fibromyalgia.

Literature Review

Personalized medicine has become a buzzword; headlines tout the new movement as one poised to revolutionize medicine (Pollack, 2005; Roan, 2008; Dreifus, 2006; Grady, 2008). Former Health and Human Services Secretary Michael Leavitt said at a conference in Washington, D.C., in 2007, "Personalized healthcare will combine the basic scientific breakthroughs of the human genome with computer-age ability to exchange and manage data" (Fox, 2007). But what exactly is "personalized medicine"? According to Woodcock, it is "nothing more than what medicine has always been at its best – the careful evaluation of the health of an individual based on the best information obtainable about the person's physical and mental state" (Woodcock, 2007).

Traditional medicine works by generating diagnostic hypotheses, which set the context for testable predictions. If the enlarged and tender liver detected by physical examination indicates hepatitis (the hypothesis), specific liver tests should be elevated (the prediction). If not, the hypothesis needs to be discarded or substantially modified (Fauci et. al, 2005). One of the cornerstones of personalized medicine is the hope that

new diagnostics may help individualize therapy and transform its scientific basis – from trial and error to treatment based on pathological insight.

Diagnosis in personalized cancer treatment

In cancer treatment, novel diagnostic tools, such as the HER2 receptor test for breast cancer and the OLIG2 test for certain brain tumors, turn the focus on specific cellular targets for drug intervention. They also provide significant predictive value for treatment response, which has been demonstrated for drugs like Herceptin and Gleevec (Woodcock, 2007). Genentech's Herceptin was the first personalized drug for breast cancer and is effective only in patients whose cancer cells produce the HER2 receptor, a protein that can be detected using approved diagnostic tests. Novartis' Gleevec, developed for CML patients but also used by patients with gastrointestinal stromal cancer, targets the genetic aberration called the Philadelphia chromosome, for which informational tests are available (Kling, 2007). But Herceptin and Gleevec have been lone players in a sluggish game. Only in recent years have a dozen or so pharmaceutical companies started developing diagnostic markers that guide prescribing. For example, the Amsterdam-based biotech firm, Agendia, offers a technology platform with 70 genes that serves as a mammaprint, or a prognostic tool for breast cancer recurrence following chemotherapy and radiation (Hayden, 2007). The UK-based biotech company, DxS, offers a tool that detects the presence of mutations predicting response to treatment with Imclone's colon cancer drug Erbitux. In part, the push to develop novel diagnostic tools came from the demand for medicines of better value, the high cost of drug failures, and the revolution in genomics (Allison, 2008; Little, 2006).

The FDA's handling of AstraZeneca's lung cancer drug, Iressa, is an illustrative case study of the significance of diagnostic tests in guiding treatment choice. In 2003, the agency approved the drug based on a mere 10 percent response rate. But in light of new clinical data that emerged two years later, the agency revoked its approval and required the manufacturer to change the drug's labeling to ensure that the drug was not given to anyone not already taking it; the data showed little overall clinical benefit. A reliable indicator of effectiveness—a biomarker—for Iressa is still unavailable, but the drug's failure prompted pharmaceutical companies to find diagnostic markers for the cancer drugs in their pipelines (Allison, 2008). It is perhaps in this vein that the president of Massachusetts-based Genzyme Genetics, Mara Aspinall, said, "Diagnostics has been an overlooked, underappreciated asset in the healthcare environment" (Kling, 2007). Diagnostics may have long been the neglected step-sibling to drug discovery, but its growing importance in cancer treatment is reflected in the employment boom in an industry that is attracting biologists, chemists, biostatisticians, engineers and computer programmers to develop diagnostics (Hoag, 2004).

One type of diagnostic marker helps in prognosis. Prognostic markers may be defined as factors—often genes or their protein products—that predict the outcome in the absence of therapy or that predict an outcome different from that of patients who receive therapy but who do not possess those gene variants or protein products. But many of the currently available prognostic markers for cancer are bedeviled by shortfalls. Many were identified in retrospective studies using available specimens instead of representative groups for different types of cancer, making them unsuitable to diagnose the wide biological variation found in tumors occurring in patients; many were discovered in

underpowered studies that had too few participants to reveal true clinical benefit; many were not validated in prospective trials; and for many, their prognostic impact was not shown to provide added clinical benefit (Duffy & Crown, 2008). Currently, only three cancer markers predicting a likely response to a specific therapy are in widespread clinical use—estrogen receptor, progesterone receptor, and HER-2.

A large number of cancer markers purportedly useful in diagnosis and screening are beset with problems of reliability and validity, in part because their diagnostic utility could not be reproduced when tested in large populations. Bias and chance plague the studies that led to the discovery of many markers, tempering the initial enthusiasm of the scientific community and media outlets (Ransohoff, 2007).

Further, some cancer biomarkers are unreliable because researchers analyzed cancerous and noncancerous tissues on separate days using machines that didn't always give reproducible results. Other biomarkers were discovered in studies in which scientists compared apples and oranges: One biomarker for prostate cancer was discovered in a study in which the researchers compared blood from 67-year-old men with prostate cancer with blood from 47-year-old women. In such studies, experts argue, bias rather than a biomarker might explain the observed differences between individuals with and without cancer (Ransohoff, 2007).

While such studies may pass enough scientific muster to sneak through the peer review process in scientific publishing, the biomarkers that they identify are unlikely to benefit most patients.

Even those biomarkers routinely used for predicting prognosis are far from perfect. Estrogen receptor, a protein used to predict response to hormone therapy for breast cancer, was discovered in a review of patient data from worldwide clinical trials. The review found that more than half of patients whose cancer cells overproduced the estrogen receptor responded to hormone therapy, while those whose cells did not overproduce the estrogen receptor had little chance of responding. That led to a widely-used laboratory test for the receptor. But oncologists have since questioned the test's reliability, citing that the test could be wrong as many as four times out of ten. Further, new evidence uncovered since the test's adoption suggests that it's not just the amount of receptor in cancer cells that is crucial for predicting prognosis but also the amount of the receptor's precursor—a molecule, called estrogen receptor messenger RNA, which carries the recipe for making the receptor. The test does not measure the amount of messenger RNA in cancer cells (Duffy & Crown, 2008).

Other quantitative tests have entered the scene since the estrogen receptor test was introduced. Oncotype DX, a prognostic test manufactured by California-based Genomic Health, measures the activity of 16 cancer-associated genes to predict the risk of metastasis—and, therefore, of recurrence—in breast cancer patients receiving the chemotherapy drug tamoxifen. Mammaprint, a prognostic test manufactured by Amsterdam-based Agendia, rummages through 70 genes in patients' tumor samples to predict the risk of cancer's recurrence in newly-diagnosed breast cancer patients (Henderson, 2007).

The FDA has approved Mammaprint for use in predicting the likelihood of cancer recurring for certain breast cancer patients, but the agency has not approved Oncotype DX, which continues to be used as a test unregulated by the FDA. Tests can be offered by laboratories without FDA permission, even as scientists work toward validating them. But both those tests have problems. Based on patients' genetic profiles, the tests either group patients into three categories—high, intermediate and low risks of cancer recurrence—or provide a specific number between zero and 100 that represents patients' risk of cancer recurrence. The test predicts this risk from the association between genetic profiles and cancer recurrence that scientists have observed among thousands of cancer patients in past clinical trials. Doctors use the risk information to decide whether a patient might benefit from chemotherapy. While patients in the low and high risk categories are likely to get an unambiguous answer to that question, patients in the intermediate risk category are left wondering whether they should undergo chemotherapy (Henderson, 2007).

Therein lie the problem and the solution. Diagnosis plays a pivotal role in cancer treatment because even small genetic variations between individual patients could mean the latest blockbuster cancer drug for a particular cell type could be a lifesaver to one patient while being lethal to another. These genetic variations may alter the behavior of cellular proteins that carry drugs to their targets, curtail enzymes that render drugs functional, block drugs from binding to their targets, change how well a drug is tolerated, and determine the overall bodily response to the drug (Abbott, 2003). Much of that variation lies in single letter changes in the genetic code, called Single Nucleotide Polymorphisms, or SNPs. These changes have been known to allow toxic cancer drugs to

linger in the body at dangerous levels instead of conferring the intended benefit. But here's the rub: For a multifactorial disease like cancer, often described as a constellation of diseases, identifying the variations that could potentially affect the patient's outcome presents a challenge of leviathan proportions (Katsnelson, 2005; Geddes, 2008).

To be sure, comprehensive studies have found a small number of SNPs as statistically strong prognostic markers for certain cancers. For example, specific SNPs in genes such as p53, estrogen receptor, progesterone receptor, BRCA2, and the proto-oncogene HER-2 have been shown to predict the risk of breast cancer and response to therapy. A few other markers are also used occasionally. Cytochrome c, a protein released by dying cells, has also been used as an indicator for ongoing cell-death induced by cancer drugs. Fragments from the cellular backbone, or cytoskeleton, have been used as signs that certain cancer drugs are producing their intended effect (Anderson et al., 2006). Robert Lipschutz, vice-president of California-based biotech giant Affymetrix, says to develop tests that guide therapy based on genetic variations, one would have to assay millions of genotypes from different patients, making the analysis unsuitable for a clinical trial setting. However, he says, chips and other sophisticated technologies could bring the detection of such genetic variation within the realm of possibility (Lipschutz, 1996). Some scientists are even proposing a follow-up to the Human Genome Project: creating global consortia to archive group and individual patient genotypes and drug-response phenotypes (Gurwitz, Lunshof & Altman, 2006).

Mining the genetic data within tumor cells is no easy feat. Researchers deploy three broad strategies aimed at finding the connections between the patterns of gene

activity within tumor cells and the cells' behavior. The first is the *data-driven approach*, in which a genome-wide analysis of gene expression, or the process by which genes produce proteins implicated in cancer, helps establish correlations between tumors and their likely response to therapy. The second is the *knowledge-driven approach*, in which tumors are probed for suspect genes based on the scientific literature. The third is *the model-driven approach*, in which the activity of genes after exposure to a specific stimulus—often a candidate drug—is used to predict response in the laboratory. Each method has its drawbacks: The data-driven approach relies on the quality of the data and the samples; the knowledge-driven approach is only as good as the state of the knowledge; and the model-driven approach might not accurately reflect what happens in tumors in the human body since the results of the approach are obtained in laboratory settings (van't Veer & Bernards, 2008).

One significant hurdle in biomarker-driven decision-making for drug manufacturers is the lack of quantitative information about how hard a target needs to be hit to obtain an optimal amount of therapeutic benefit. For example, the right dose of the chemotherapeutic drug for acute lymphoblastic leukemia is determined based on the patient's thiopurine methyltransferase gene. When administered, the drug is inactive and must be transformed in the patient's body into its active form. That transformation, brought about by the patient's methyltransferase enzyme, depends on how much of the enzyme the patient's cells make, and thus the drug depends on the activity of the gene that produces the enzyme. But the number of cancer drugs for which targeted dosing information is available is small (Lesko, 2007). Even when all else works with clockwork precision—as is almost never the case—cancer cells often develop resistance

to individual drugs, a problem that might be overcome by administering drug cocktails which contain a mix of different drugs; when one drug fails, another takes over for a while (Ikediobi, 2008; Geddes, 2008).

Currently, genomic analysis of patient samples occurs in no more than 30 percent of early-stage drug development programs, according to a report on personalized medicine from the United Kingdom's Royal Society (Branca, 2005). The challenges to developing useful cancer markers are many, but there is reason for optimism. Systematic evaluation of candidate markers in distinct phases, adherence to evidence-based guidelines, and attention to appropriate study designs could lead to the development of truly useful markers (Ransohoff, 2007; 2008).

So, some scientists suggest that drug developers follow a pharmacologic audit trail, consisting of a series of questions, while designing tailor-made cancer drugs: What is the status of the molecular target in the patient? Will enough of the drug be retained in the patient's blood to hit the target? Will the drug be specific to the target? Will hitting the target disrupt the right downstream biochemical pathways? Will that disruption produce the intended biological effect? Will that effect result in a desirable clinical response? (Collins & Workman, 2006).

Those questions are among the hardest to answer. That's why Mervyn Turner, the chief strategist for Merck & Co., recently said, "The early stage of drug development has been democratized, but late stage clinical development is a tyranny" (personal communication). Further, segmenting patient populations to reduce genetic heterogeneity is challenging to drug companies, which typically prefer to target the largest possible

markets. Studying why some patients respond to certain drugs is a gamble for drug-makers who have no way of knowing the size of the responder population before millions of dollars are spent (Million, 2006). That said, patient genetic information could help pharmaceutical companies design better clinical trials, weeding patients progressively and reducing the overall cost of developing safer, more effective drugs (Marshall, 1997; Berenson, 2005).

Stumbling blocks to personalized cancer treatment loom large in the minds of patients and physicians, too. Many of the new-wave diagnostics are expensive. Compared to the $48 that U.S. Medicare pays for a HER-2 test for response to herceptin for breast cancer treatment, some novel diagnostic tools can cost in the thousands of dollars (Baker, 2006). While some insurance companies are willing to pay a higher price for novel diagnostics because they potentially reduce the overall cost of cancer treatment, many cancer patients don't have private insurance (Kling, 2007; Pollack, 2004). The U.S. health care system is too fragmented to integrate predictive risk information into treatment over an individual's lifetime (Deverka, Doksum & Carlson, 2007). Constrained by the amount of time available at the point of care, the average physician might be unable to embrace the use of diagnostics—assuming the tests are proven reliable and valid—while providing care (Levy & Young, 2008). Issues of confidentiality, privacy, malpractice, and genetic discrimination riddle the new movement (Reilly, 2001).

Diagnosis in infectious diseases

Many clinicians are familiar with a scenario in which a previously healthy patient develops a life-threatening illness bearing the hallmarks of infection but has negative

diagnostic test results. In 1996, the Centers for Disease Control and Prevention (CDC) launched the Unexplained Deaths Project as a systematic effort to analyze such cases. The project's early reports found that fewer than two per 100,000 people in the U.S. are affected by such illnesses and that molecular analysis revealed the signatures of pathogens in those patients (Relman, 1999).

While personalized medicine, the notion of tailoring therapy based on patient characteristics, has been slow to integrate novel diagnostics into routine clinical practice, the study of infectious diseases has benefited from an explosion of diagnostic technology. Surveys have indicated that less than one percent of all known microorganisms can be cultivated in the laboratory; the rest require the use of molecular methods for identification. This situation occurs partly because scientists are unaware of the precise environmental conditions that support the growth of microbes and are, therefore, unable to replicate them in the laboratory.

Recent improvements in technology have revolutionized research and clinical management of infectious diseases. The Human Genome Project and efforts to unravel the genomes of pathogens have provided insights for developing tools to detect elusive and novel pathogens. One of those tools, called the microarray, is widely used in research settings because it allows the rapid, simultaneous analysis of thousands of genes. A microarray may be defined as a solid substrate, such as a silicon wafer or a glass slide, on which short strings of genetic material from the pathogen, called probes, are attached. Matches between the genetic material found in a patient's sample and the strings immobilized on the substrate are used to determine the identity of the pathogen afflicting

the patient (Bryant, Venter, Robins-Browne & Curtis, 2004). The probes, which are short strings of the chemical compounds that compose genetic material, are complementary to thousands of genes of both known and unknown function. Depending on the object of the analysis, tailor-made microarrays contain probes that are designed to detect one kind of pathogen over another. The process works thus: DNA prepared from a patient's body fluid or tissue sample is passed on the microarray. A scanner picks up any matches, which are then analyzed to reveal the genetic identity of the DNA found in the patient's sample (Bryant et al., 2004; Ramsay, 1998). The choice of probes for a microarray depends on the sample being tested: It would make little sense, for example, to test DNA from a patient's gastrointestinal sample on a microarray containing probes from respiratory viruses. Microarrays can be used to identify a pathogen, discover novel pathogens, predict outbreaks, track the evolution of pathogens over time, and analyze the virulence and invasiveness of pathogens. They can also be used to predict the development of resistance to antimicrobial drugs among known pathogens (Clewley, 2004).

Today, most microarrays used in clinical settings are developed by a small number of biotechnology firms, like California-based Affymetrix and Massachusetts-based Millenium Pharmaceuticals. Some researchers put together home-made microarrays for specific needs (Mikhailovich, Gryadunov, Kolchinsky, Makarov & Zasedatelev, 2008). The high sensitivity of microarrays allows the speedy diagnosis of infected patients, especially when the levels of the pathogen in the patients' bodies are low (Mahony, 2008). Microarrays are now routinely used to detect respiratory bacterial

pathogens, respiratory viruses, papillomaviruses, gastrointestinal viruses, and potential biological warfare agents (Loy & Bodrossy, 2006).

One striking example of the use of microarrays was in the identification of the SARS virus as a novel member of the family of coronaviruses. In 2003, Joseph DeRisi, a molecular biologist at the University of California, San Francisco, helped the CDC confirm the identity of the virus using a tailor-made microarray that came to be widely known as the Virus Chip (Elias, 2003). DeRisi's chip, an ordinary 1-by-3 inch microscopic glass slide on which 22,000 different viral probes had been spotted, could simultaneously screen for more than 1,000 different families of viruses, representing virtually every virus known to biologists at the time. Because viral DNA from patient samples will bind to the probes even when there isn't a perfect match, new relatives of known viruses can be identified as belonging to a particular family ("Gene chip for viral discovery," 2001). Former CDC director Dr. Julie Gerberding hailed the device as "the absolute state-of-the-art probe for viral genes" (Russell, 2003). DeRisi designed and built the robot that made the chip, and with help from a friend at the Massachusetts Institute of Technology, he wrote the software to automate the robot.

After the initial success with the SARS virus, DeRisi used the device to identify the virus that was causing a novel wasting disease in parrots, macaws, and cockatiels. He decided not to patent his chip, preferring instead to disseminate the technology (Dreifus, 2008). His chip has since been used to identify a virus, previously found only in mice, as the cause of prostate cancer in some men with a specific genetic defect known to confer

susceptibility to the disease (Maugh, 2006; Elias, 2006). DeRisi has also used the chip to detect respiratory viruses in a clinical setting (Wang et al., 2002).

Despite the few success stories with microarrays, less than nine percent of all manufactured arrays are used in diagnostics, the rest being used for basic research (Striebel, Brich-Hirschfeld, Egerer, Foldes-Papp, 2003). Aside from the high cost, the difficulty of making microarrays with a sufficiently large number of probes is a hurdle to researchers. Furthermore, the quality of microarrays affects the reproducibility of their performance. That's why the FDA created the Microarray Quality Control consortium in 2005 (Jordan, 2007).

Although microarrays have helped researchers make inroads into microbial diagnostics, they have not changed the diagnosis of emerging infections, such as drug-resistant tuberculosis and malaria. Tests for pathogens causing these diseases are antiquated, inaccurate, and inadequate. For tuberculosis, the inadequacy of the standard diagnostic tests—sputum microscopy, skin testing, and radiography—is well documented. These tests suffer from low sensitivity, poor predictive value, and long processing times. Evaluation of drug resistance in tuberculosis patients takes at least four weeks, delaying treatment and sometimes leading to the administration of ineffective drugs that worsen the problem (Mikhailovich et al., 2008). But the availability of the complete genomic sequence of *Mycobacterium tuberculosis* has now created opportunities for developing novel diagnostic tools for the disease.

For malaria, microscopic evaluation of blood samples is not only difficult but highly variable depending on who performs the diagnosis. Experienced microscopists

disagree on their diagnosis of up to a third of all microscopic slides (Perkins & Small, 2006). But microarrays for the malarial parasite *Plasmodium* are just beginning to be developed in research labs. Indeed, DeRisi pioneered the development of a chip that could shed light on the developmental stage of the parasite in a patient's blood, gene activity within the parasite in the blood, and the likelihood of drug resistance. He suggests that investigators' unfamiliarity with the details of microarray technology might be an initial deterrent to the widespread adoption of this technology in the laboratory. However, he predicts that it won't be long before every parasitologist will have easy access to malaria chips in a reliable and affordable form (Rathod, Ganesan, Hayward, Bozdech, DeRisi, 2002).

Diffusing the technology among researchers is not the same as promulgating its use among clinicians. Developing countries, in which diseases such as malaria and tuberculosis are widespread, can hardly afford the high-priced technology. Hence, public-private partnerships may be the solution. For example, The Foundation for Innovative New Diagnostics based in Geneva, Switzerland, is one such entity, whose goal is to identify the most promising diagnostic candidates for diseases of the developing world; accelerate development, testing, approval, distribution, and incorporation into routine clinical care; and help contain neglected public health scourges (Perkins & Small, 2006).

DeRisi's technology has not yet found its way into the clinic because of its cost. But it's not because the chip would be too expensive that venture capitalists are loath to invest in it. It's because it's too cheap: A single commercial version of the chip would cost $50 per test. That's too little return on investment to interest investors, who typically

chase diagnostic tests that cost $3,000 a run (Levine, 2006). But a cheap diagnostic test that provides significant clinical benefit might make up in volume if used in cases where millions are affected. Further, such a tool could lower health care costs by reducing the overprescription of antibiotics and by curtailing drug resistance. DeRisi is now participating in the launch of a new center for the diagnosis of emerging infections at the University of California, San Francisco. He hopes that the use of his chip technology at the center would be a step toward integrating the use of microarrays in the diagnosis of emerging infections in the clinic and in public health settings. The challenges to that effort are many, but he predicts it won't be long before they are overcome (Dahlberg, 2008).

The tyranny of non-diagnosis

Diagnostic techniques may have begun to transform medicine, but for some patients, the transformation yields few answers in their search for names for conditions without clearly identifiable physiological bases. These undiagnosed conditions may manifest themselves differently but are often unified by a common narrative: widespread pain, fatigue, flu-like symptoms, and a loss of zest. Chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome are a few examples of diseases for which the physiological bases are hotly debated. Patients in search of a diagnosis for mysterious conditions are often confused by a lack of consensus in the medical community. While some doctors suggest that it's only a matter of time before the underlying pathology surfaces, others argue that many of these conditions shouldn't be treated as medical disorders because they have no known organic cause and that they are better managed by

psychotherapy. Allegations and actual instances of disease mongering by drug makers have only fueled the debate (Hadler, 2008). In May 2008, the NIH launched its *Undiagnosed Diseases* program to help patients in search of a diagnosis. The program, supported by 25 scientists from the NIH Office of Rare Diseases and the National Human Genome Research Institute, invites applications from patients who have waited for years for a diagnosis despite ongoing consultation with a primary care physician (Keim, 2008). The debate over whether such an effort is worthwhile rages on, as patients continue to be whipsawed by doubt and optimism.

On one side of the debate, experts argue that technological handicaps and physicians' approach to disease may hinder accurate diagnosis. In his book *Second Opinions*, Dr. Jerome Groopman explains how clinical decision making would be a well-defined, scientific exercise in a predictable world. He argues that physical and emotional responses to each illness can be as varied as the personalities of the afflicted. "This means that diagnosis cannot be strictly bound by generic recipes, but must be made individual," he suggests. He undertakes a lengthy treatment of the phenomenon of reactivation of exotic microbes years after infection as a cause of bizarre, episodic symptoms characterized by fever, fatigue, and fogginess. He provides a brief description of the weekly clinical conferences where Harvard specialists discuss the toughest cases by creating lists of possible causes. Then, he introduces the concept of idiopathy – "a wastebasket term applied to disease conditions whose origins were not known." He cautions against the use of the term, which might imply that "you are satisfied with your ignorance and ready to stop searching further for a discrete cause" (Groopman, 2007).

Some scientists note that the art of making a diagnosis has its shortfalls. Using 50 instances of pathology examined at medical conferences, Doctors Eddy and Clanton distill the essence of diagnosis to the following: "aggregation of groups of findings into patterns, selection of a *pivot,* or key finding, generation of a cause list, pruning of the cause list, selection of a diagnosis, and validation of the diagnosis." Although its systematic and often thorough nature makes pattern recognition a valuable technique for honing in on a patient's condition correctly, they suggest that pattern recognition ignores the inability of the human mind to juggle and weigh multiple probabilities on the spot (Eddy & Clanton, 1982).

On the other side, experts argue that social construction and patients' inability to cope with innocuous symptoms underlie many mystery disorders (Hadler & Greenhalgh, 2004). Rheumatologist and author of the book, *Worried Sick,* Dr. Nortin Hadler argues that putatively scientific treatments for conditions without clear biological bases might only thrust patients deeper into a downward spiral of distress. "All the while, the treatment act is plying the patient with intimations to the pathophysiology of their nociception. That is how the person suffering persistent widespread pain learns to be a patient with Fibromyalgia (FM)… The patient is changed forever. Their narrative is laced with the clinical heuristics they have learned, which they can recite with objectivity that approaches dispassionate," (Hadler, 2003).

Further, doctors' approach to clinical diagnosis might perpetuate such disorders. Dr. Sherwin Nuland, a professor of surgery at Yale University and author of popular non-fiction books, recounts the writings of French literary savant Voltaire and the first

modern physiologist Claude Bernard to illuminate an axiom doctors must grapple with throughout their professional lives: "[a physician] should never allow himself to forget for a moment how it can lead him astray while caring for any one sick person, whose situation may present riddles that differ from everything else he has learned at the bedsides of so many others." Nuland discusses seven important factors that govern physician judgment during the process of diagnosis: the urgency of the situation, the evolutionary pattern of the disease in the individual in question, the facts of the pathology as they unravel, inferences made from the facts, the patient's emotional and biological response to illness, the circumstances of the patient-physician encounter, and the physician's own sociocultural baggage. He suggests that the rush to label a disease might sometimes cause physicians to treat psychosocial problems as medical disorders (Nuland, 2008).

Amid the debate, patients with undiagnosed disorders suffer. In the book *The Lonely Patient*, physician-writer Dr. Michael Stein takes readers into the emotional landscape of patients battling illnesses. He tells the story of disease from the patient's standpoint, giving readers a glimpse of the rollercoaster ride patients are unwillingly thrust into from the moment they are given a diagnosis. This ride is marked by feelings of betrayal, anger, loss, terror, and loneliness. The patient's story also explains the importance of paying mind to the "idiom of the ill."

Stein writes, "Each patient's emotions seemed just slightly out of my reach. I was inarticulate about the patient's experience of illness, but I was also holding back, in part because of my training and in part because I believed I didn't have the right to ask or

intrude." Stein suggests that the clinical information-gathering process, the physician-patient interview, and clinical diagnosis proper may be key factors in addressing patients' problems (Stein, 2008).

Some scientists suggest that classical theories of persuasion and rhetoric may help physicians evaluate patient complaints for which no objective evidence exists and which depend uniquely on the persuasive power of patients to be taken seriously (Segal, 2007). They propose ways in which physicians might convince patients that nothing is wrong with them and that medical intervention would possibly cause more harm than good.

The journey through this two-way street—towards and away from diagnostic labels—is fascinating at the very least, and exasperating at best. On the one hand patients trying to find a label for their own conditions are called by some doctors "anxiety-ridden," "know-it-all," "refuseniks," and "malingerers." On the other hand are experts who believe that labeling misery is hardly a solution to such mysteries (Segal, 2007; Hadler, 2003).

Research Questions

As the literature review shows, there are a number of ways in which diagnosis plays a crucial role in the practice of medicine, in particular in the development of tools for personalized medicine, in the treatment of infectious diseases and in tackling controversial diseases. A survey of the mainstream media reveals that many stories merely skim the topic. The purpose of this series of articles, which would be suitable for a publication such as *Scientific American*, is to elucidate the central role of diagnosis in

medicine and to show how advances in diagnostic technology have improved the treatment of certain diseases while yielding little benefit to the treatment of others. The thesis specifically seeks to answer:

1. What are the challenges to developing diagnostic markers for truly personalized cancer therapy?

2. How have recent advances in molecular diagnostics transformed the treatment of infectious diseases, especially emerging infections caused by novel viruses?

3. What happens when doctors cannot diagnose a disorder? What is the plight of patients suffering from disorders whose very existence is controversial?

Methodology

To answer these questions, the series is divided into three stories. The first feature story in the series serves as a piece of explanatory writing that presents the nuts-and-bolts of diagnosis in personalized cancer treatment and the challenges to developing tailor-made medications. It attempts to explain the significance of diagnostic markers while addressing the challenges to developing them. The story on biomarkers for cancer treatment presents case studies of patients receiving such treatments with interviews with cancer researchers at leading institutions providing personalized care.

The second feature serves as a trends-cum-analysis piece that offers an in-depth look into the state-of-the-art of diagnosis of infectious diseases. It looks at diagnostic

chips for the diagnosis of emerging infections, including interviews with the pioneer of the Virus Chip technology, Joseph DeRisi, a molecular biologist at the University of California, San Francisco, and Dr. Charles Chiu, an infectious diseases specialist, who will head the new center for the diagnosis of emerging infections at the University of California, San Francisco.

The third and final feature of the series poses the question: *What happens when a disease cannot be diagnosed in the clinic?* This feature story looks into the life of a patient battling an undiagnosed condition. It serves as a representative profile that also presents the long festering debate over the treatment of mystery illnesses. To illustrate a story on mystery illnesses, interviews focus on the experience of 24-year-old Kerry Brewer of Cary, North Carolina, the daughter of a former government attorney, who went from being a successful track-and-field athlete to what some might call a professional patient. In the last two years, she has seen more than 30 doctors and has taken a dizzying list of medications, to little avail. Diagnosis still eludes her. This piece is written in the form of narrative nonfiction instead of following the traditional journalistic style. Narrative nonfiction applies the techniques of fiction—characterization, detail, description, and extended anecdotes—to journalistic accounts. This story includes interviews with Brewer's doctors and independent experts who provide context and address the broader, universal theme of elusive diagnosis.

In a fourth chapter, the author includes his observations on the importance of diagnosis in three subject areas -- personalized cancer treatment, emerging infections and controversial illnesses. Also included are some recommendations for additional stories as

well as guidance to reporters who take on the task of writing about complicated medical topics for lay audiences.

CHAPTER II

BIOMARKERS IN CANCER TREATMENT

Editor's Note: This series of feature stories consists of three articles on the role of diagnosis in modern medicine. Traditional and modern methods of diagnosis affect treatment choices for patients and have a big impact on health care delivery and costs. The first story explains the diagnostic challenges to tailoring cancer treatment to patients' genetic makeup. The second story discusses the role of cutting-edge diagnosis in treating infectious diseases, and the third explores the controversy surrounding the diagnosis of fibromyalgia. Together, the stories represent three facets of diagnosis – the challenges, the promise and the conflicts surrounding this essential part of medical practice. This is the first of three stories.

One morning in August 1999, Patricia Spears, 50, noticed a lump on her breast and another in her armpit. Two weeks later, the lumps were still there. A research technologist at North Carolina State University in Raleigh, N.C., Spears was almost sure of the diagnosis. A visit to oncologist Dr. Becky Campbell at Rex Cancer Center in Raleigh confirmed her fears.

"The ultrasound and mammogram revealed that what I had was most likely a malignancy," Spears says. Two days after the mammogram, Campbell ordered a biopsy

of the lump on Spears' breast, but her doctor didn't think there was any need to wait for the results before beginning treatment.

"My oncologist said, 'It looks like a duck, quacks like a duck, so it is a duck,' and suggested I start chemotherapy as soon as I could get an appointment," Spears says.

A week later, Spears started chemotherapy, a mix of drugs – adramycin, cytoxan and taxol – commonly prescribed to breast cancer patients at the time. The regimen worked, although Spears endured a range of side effects, including nausea, fatigue, pain, rashes, and an anaphylactic reaction to taxol. The lumps in her breast shrank before disappearing eight weeks after her diagnosis.

Spears' biopsy report came back a week after she had started chemotherapy. It showed that two proteins implicated in breast cancer—estrogen receptor and progesterone receptor—were absent in her cancer cells. The report also showed that her cancer cells overproduced HER2, a protein that promotes the growth and multiplication of cancer cells, making the cancer aggressive and difficult to treat. Spears' doctor didn't switch Spears' therapy based on this genetic information because there weren't better alternatives to the cancer drugs Spears was taking.

That was in 1999.

Today, the same information would have put Spears in a category of patients eligible to get the cancer drug trastuzumab, known by Genentech's brand name Herceptin, and might have spared her the slew of side effects that she endured. Herceptin is an antibody that targets the HER2 protein in cancer cells, blocking the protein's

function and sending the cancer cells on the fast track to death. The antibody is given alone or along with chemotherapy to patients whose tumor cells overproduce the HER2 protein. According to the National Cancer Institute, Herceptin slashed by half the risk of cancer returning in patients who took the drug along with chemotherapy compared to patients who got chemotherapy alone. However, the drug has caused congestive heart failure in some patients.

"At that time, Herceptin was only given to women with metastatic disease, so I didn't qualify for that. Today, oncologists know that these kinds of tumors respond better to Herceptin," says Spears, whose cancer hasn't recurred.

Herceptin is among a growing class of targeted cancer drugs that includes other bestsellers such as Novartis' Gleevec for stomach cancer, Genentech's Avastin for breast cancer, and Genentech's Tarceva for lung cancer. Some patients and doctors have hailed these drugs as harbingers of hope for cancer patients because the medications work by exploiting molecular differences between cancerous and normal cells. Others have reviled the drugs as medications that help patients eke out a few extra months of life at a huge cost.

To develop some of these drugs, researchers relied on specific molecules in cancer cells that help scientists diagnose cancer. These molecules, called biomarkers, lie at the heart of modern cancer treatment.

Biomarkers are essentially fingerprints. They may be proteins found in the blood or tissues of cancer patients, or genes in cancer cells. Scientists take samples of cancer

from different patients to develop a fingerprint for each cancer type. The hope is that the fingerprint—a basis with which to compare new patient samples—would help doctors group patients based on the kind of cancer they have.

Thus, doctors can use biomarkers to detect early-stage cancer before patients experience symptoms and to assess the likelihood that a cancer will recur. In addition, doctors use biomarkers to group patients for treatment and to predict patients' response to treatment.

Biomarkers are among oncologists' vital tools in the war against cancer, but a common problem besets most biomarkers: They are unreliable.

While scientists have discovered a handful of biomarkers for different types of cancer, most have not found widespread use in the clinic because their usefulness has not been demonstrated in clinical trials involving large numbers of cancer patients. Most biomarkers were discovered in studies of tumor samples from patients by comparing the tumors with tissues from normal individuals. But here's the rub: The tumors and normal tissues used for biomarker discovery were sometimes handled differently or came from different clinics.

Dr. David Ransohoff, a professor of medicine at the University of North Carolina at Chapel Hill, says scientists have trouble determining the uniqueness of each individual's cancer at the genetic level. No one knows all the ways in which a given kind of cancer could manifest itself among patients. So, Ransohoff says, the biomarkers in use aren't truly representative of the cancer types for which they were developed. That's

because laboratory researchers didn't always use enough samples of tumor tissues for each type of cancer during the discovery of biomarkers. "Depending on which patients were chosen for specimen collection the markers may be meaningful or totally meaningless," Ransohoff says.

Ransohoff says a more reliable way to discover cancer biomarkers would be to follow a large group of healthy individuals over time and periodically collect samples from them. Scientists could then compare the cancer cells of those who develop cancer with the cells of those without cancer to pinpoint differences.

Dr. Neil Hayes, a UNC-Chapel Hill oncologist, says obtaining enough tumor tissue is the number one hurdle facing the discovery of biomarkers. Hayes participates in a nationwide consortium—Cancer Genome Atlas Network—to catalog all the genetic abnormalities in cancer. The network has started work on a kind of brain tumor called glioblastoma. Scientists in the network have set up in Phoenix, Ariz., a repository of cancer tissues from patients across the country. The repository houses tissues and blood samples from thousands of cancer patients, but that's far fewer than what scientists need to represent the genetic variability occurring in populations, Hayes says.

Developing truly useful biomarkers might require collaboration between a number of institutions and regulatory agencies. "Biomarker development has received much less attention than drug development," Ransohoff says. There are no existing guidelines for developing biomarkers into tools useful in the clinic. "There is not much consensus in this field. It's a very difficult area, and a lot of people are wandering around in this desert," he adds.

For predicting response to drugs, Ransohoff says, drug companies could develop biomarkers concurrently with drugs. “It’s easy to piggyback studies of prognostic markers onto the clinical trials of cancer drugs,” he says.

“It’s a chicken and egg situation. To develop the drug, you often need a marker, but developing the marker ahead of the drug can be a real challenge,” says Sharyl Nass, a breast cancer researcher at the National Academy of Sciences, who was one of the authors of a report on cancer biomarkers published by the Institute of Medicine in Washington, D.C.

Dr. Kimberly Stegmaier, a pediatric oncologist at Dana-Farber Cancer Institute in Boston, Mass., is trying to combine biomarker and drug discovery in the laboratory. Stegmaier identified a small chemical compound that altered the activity of certain cancer-associated genes in the blood cells of patients with a rare but fatal form of childhood leukemia, called acute myeloid leukemia, or AML. Children with AML have a survival rate of 50 percent. She is now testing the compound in a clinical trial for AML patients.

Stegmaier identified the genes that the compound targeted by using a technology, called microarrays, that sifted through thousands of genes in normal and cancerous blood cells and spotted differences between the two cell types.

“We asked ourselves whether we could use gene [activity] as a biomarker, in essence, in response to a chemical compound in the laboratory. This is not the classic way of using biomarkers in patient samples to predict response to therapy,” Stegmaier

says. “The ultimate hope is that we would be able to translate our findings to predict gene [activity] patterns that would predict response to drugs in the patient.”

If such a drug were to prove safe and effective in trials, it could significantly extend the lives of children with AML.

A number of challenges temper that hope. Stegmaier says one of the biggest challenges is determining how unique each individual’s cancer is. Further, she echoes Ransohoff’s concerns, “Technical issues with sample handling and processing could cloud data interpretation. That’s a huge problem.” She says pediatric cancers often pose an additional problem: Patients’ tumors provide too little tissue for large-scale studies of biomarker discovery.

Despite these hurdles and the lack of guidelines, scientists everywhere are forging ahead with efforts to discover new cancer biomarkers. Only a handful of those freshly minted biomarkers are likely to be validated, and an even smaller number is likely to reach the clinic in the form of approved diagnostic tests.

“One of the obstacles is that the FDA doesn’t have clearly delineated pathways for biomarker validation, to say nothing of drug-biomarker combinations. They’re trying to figure it out as they go. It’s not yet clear what they should be having drug companies do in this regard,” Nass says.

That’s why, she says, the Institute of Medicine report recommends that federal agencies, such as the National Institutes of Health, the Centers for Medicare and Medicaid Services, and the FDA work with academia, the drug and diagnostics

industries, and health insurers to create guidelines for biomarker development, validation and use.

Such a set of guidelines may not become available in the near future. But some patients like Patricia Spears are doing fine despite the lack of biomarker-driven decision making during treatment.

Spears is now cancer-free. Her breast cancer never returned after her chemotherapy. While Spears was undergoing treatment, her mother was diagnosed with breast cancer. That prompted Spears to undergo a bilateral mastectomy a month after her treatment ended.

“My doctors had spotted a pre-cancer in my other breast, and I really didn’t want to get diagnosed again,” she says.

Spears now conducts support groups in Raleigh for women with breast cancer. “Some of these new prognostic and predictive tests may be imperfect, but they have made a difference. It eases the minds of patients when they know their risk of recurrence,” she says. “Knowing whether a patient might respond to chemo makes a huge difference.”

CHAPTER III

MICROARRAYS AND INFECTIOUS DISEASES

Editor's Note: This series of feature stories consists of three articles on the role of diagnosis in modern medicine. Traditional and modern methods of diagnosis affect treatment choices for patients and have a big impact on health care delivery and costs. The first story explains the diagnostic challenges to tailoring cancer treatment to patients' genetic makeup. The second story discusses the role of cutting-edge diagnosis in treating infectious diseases, and the third explores the controversy surrounding the diagnosis of fibromyalgia. Together, the stories represent three facets of diagnosis – the challenges, the promise and the conflicts surrounding this essential part of medical practice. This is the second of three stories.

In December 2005, Dr. Bruce Patterson, director of virology at Stanford Medical Center in Palo Alto, Calif., admitted a 28-year-old woman to the hospital for an open lung biopsy – a surgical procedure to obtain a piece of lung tissue with the aim of arriving at a diagnosis.

Weeks earlier, the woman had seen her primary care physician at Stanford for fever, sore throat, shortness of breath and cough that persisted for 10 days – classic symptoms of a respiratory tract infection. Her physician suspected a bacterial infection

and prescribed antibiotics. Despite taking antibiotics for three days, the woman's symptoms rapidly worsened. She developed a high fever and had difficulty breathing.

On the fourth day, she was rushed to the emergency department. X-rays and CT scans of her chest showed fluid accumulating in her lungs. To relieve her symptoms while waiting to determine the cause of the infection, the woman's doctors gave her antibiotics—ceftriaxone and doxycyclin—followed by the antiviral medication Tamiflu, the antifungal drug amphotericin, and steroids. The woman's symptoms persisted. In addition, diagnostic tests for common disease-causing bacteria, fungi and viruses revealed no infectious agents in her blood, sputum or lung fluid. That's when Patterson decided to perform a lung biopsy.

The biopsy shed no light on the cause of the condition.

As the mystery deepened, Patterson sent samples of bronchial fluids from the woman's breathing tube to the lab of molecular biologist Joseph DeRisi at the University of California, San Francisco's Mission Bay campus.

The lab, now called the Center for Virus Discovery and Diagnosis of Emerging Infections, is a collaborative effort between DeRisi and Dr. Charles Chiu, a UCSF infectious diseases specialist. Scientists at the lab combine modern methods of DNA analysis with computer algorithms to help doctors discover previously unknown human viruses. The discovery of these viruses, which sometimes cause emerging infections, hinges on a technology called microarrays.

In 2003, DeRisi successfully used microarrays to confirm the identity of a then novel coronavirus that had killed more than 50 people in Southeast Asia and sickened more than a thousand others. The virus led to the much-publicized SARS epidemic. That initial success with microarrays led the former director of the Centers for Disease Control and Prevention, Dr. Julie Gerberding, to call microarrays "the absolute state-of-the-art probe for viral genes."

A virus microarray is a glass slide onto which scientists have spotted thousands of snippets of known viral DNA sequences. To determine the cause of an infection, scientists take genetic material from patients' tissues or body fluids and pass them on a virus microarray. If the microarray picks up a previously unknown virus that has a genetic similarity to a known virus, scientists can isolate the suspect virus and try to link it to the patient's symptoms.

Patterson, the Stanford virologist who was treating the woman with the mysterious ailment, was aware of DeRisi's work with microarrays. He turned to DeRisi in the hope of getting an answer. DeRisi and Chiu had never met the woman, but by passing her lung fluid on their microarray, they found what they thought to be the explanation for the woman's illness.

"There was a clear signature for one virus in the woman's bronchial aspirate, and it happened to be human parainfluenza virus Type 4," Chiu says.

That discovery was not groundbreaking because scientists were aware of the virus. But the scientists were surprised to find parainfluenza Type 4 because it was not

known to cause anything more severe than a common cold in healthy individuals. Parainfluenza Type 4 was not one of the usual suspects for a severe upper respiratory tract infection.

Follow-up tests at UCSF detected antibodies to the virus in the woman's blood. Now that doctors knew what to look for, they could see portions of the virus in her lung tissue. Other tests failed to identify any other bacterial or fungal pathogens that could have explained the woman's symptoms.

Later Chiu would document the case as the first instance of parainfluenza Type 4 virus causing severe bronchiolitis accompanied by pneumonia in a previously healthy patient. In October 2006, he published his findings in the journal Clinical Infectious Diseases.

The woman improved after 26 days of care in the hospital that included some time on a ventilator.

Had the results of the microarray analysis been available weeks earlier, doctors might have spared the patient the slew of medications, diagnostic tests and lung biopsy, Chiu says.

"Open lung biopsy is a high risk procedure that carries a mortality rate of about five percent. The woman needed the procedure because her doctors were unable to make a diagnosis using any of the existing diagnostic tests on her body fluids," says Chiu.

The study of emerging viral infections helps doctors discover previously unknown viruses that cause illness and helps doctors identify well known viruses—like

parainfluenza Type 4—responsible for unusual diseases. Researchers have implicated viruses in conditions that were not believed to have a viral cause for many years, such as meningitis, encephalitis and even certain kinds of cancer like liver cancer, cervical cancer and B cell lymphomas. Novel or not, emerging viral infections have taken tremendous tolls on public health in the past. These emerging infections include Ebola virus, Marburg virus, Severe Acute Respiratory Syndrome (SARS) virus and the avian flu virus.

"You cannot think rationally about either vaccine development or antiviral drug development without a knowledge of the complement of viruses that are involved in a given condition or outbreak," says Don Ganem, a UCSF microbiologist, who published in 1996 the first electron micrographs of the virus causing Kaposi's sarcoma in HIV-infected gay men.

Traditionally, novel viral pathogens are discovered by growing the viruses in host cells in laboratory dishes or by analyzing the viruses in patient samples. Researchers use molecular methods such as direct fluorescence antibody staining (DFA), in which a fluorescent antibody against a known virus is used to detect the presence of the virus in patients' samples, and polymerase chain reaction (PCR), in which scientists probe the DNA of patients' samples for the presence of a small set of known viral gene sequences.

Those methods have pitfalls. Many viruses cannot be cultured easily, and those that can be cultured take weeks to reproduce and provide enough material for analysis. Scientists do not always know the type of host cell that can support the laboratory culture of a given virus.

Both DFA and PCR depend on the use of specific tools, such as antibodies and DNA fragments, to look for known viruses. Those tools often fail to detect a novel virus that's sufficiently different from the viruses for which the tools were developed. In addition, the traditional methods are time-consuming and expensive, making them undesirable for use when hundreds of patient samples are involved.

"There is a real need for broad spectrum tests to capture the diversity of viral pathogens. There are only three or four different types of diagnostic tests, and they're not sufficient," Chiu says.

That's where DeRisi's microarray technology enters the picture. "The lesson we learned during the SARS outbreak is that we are in a new era of molecular diagnostics. Instead of spending months to years looking for viral pathogens, one could use microarrays to identify and to sequence viruses associated with disease in literally matters of days," DeRisi says.

Microarray technology allows scientists to detect in patients' samples "every virus that's ever been discovered and more," DeRisi says. His microarray chip is a 1-by-3 inch glass slide spotted with more than 20,000 tidbits of nucleic acid bar codes for all known viruses. That's about 2,000 different viruses.

In a matter of hours, genetic material from a patient's sample is prepared in the lab. Small fluorescent dye molecules are attached to the patient's genetic material which is then passed on the microarray chip. The suspect genetic material is incubated with the

chip in an oven for several hours during which time it binds to the viral bar code(s) with which it has genetic similarity. The chip is then washed.

If the suspect genetic material did not bind to any viral bar codes, it gets washed away. But if the suspect genetic material matches one or more of the codes, it remains on the chip along with the attached fluorescent dye. The chip is then passed through a scanner that captures the fluorescence. Computer software translates the fluorescence into a specific nucleic acid sequence, a road map that helps confirm the identity of the underlying virus. Using the microarray, about 400 patient samples can be analyzed within 24 hours, a rate at least 10 times faster than that of traditional diagnostic methods for viruses.

To date, DeRisi has used virus microarrays to detect a mouse retrovirus implicated in prostate cancer in men with a specific genetic defect, to detect a livestock virus that was causing a wasting avian flu in parrots, macaws and cockatiels, and to detect a novel human virus that caused intestinal disease.

“An important caveat to this technology is that if there is a completely new virus—one that has no relationship to any known family of viruses—our chip has no capability of detecting it,” DeRisi says. The likelihood of running into just such a virus—the only one of its kind—is impossible to calculate because scientists don’t know precisely what percent of human viral pathogens have been charted or how fast viruses evolve, he adds.

For using the chip commercially and for meeting insurers' payment guidelines, DeRisi would need endorsement from the federal government. To get approval from the Food and Drug Administration for the use of his microarray technology for the detection of viral pathogens in the clinic, DeRisi would need to demonstrate how sensitive and specific his arrays are.

Sensitivity is a measure of the minimum number of viral particles needed for the test to detect the virus in a patient's sample. Specificity is a measure of the frequency with which the test correctly identifies the virus that it is designed to pick up. Both those measures apply to diagnostic tests that look for specific targets, such as tests for HIV. But DeRisi's microarray device looks for unknown targets. That means it's unlikely that he would be able to provide the kind of sensitivity and specificity data that FDA regulatory authorities require for approval.

"When you have multiple viruses involved, there's no practical way to do a positive control for the test of every single virus on earth. It's infeasible," DeRisi says.

That's why DeRisi and Chiu want to make the microarray tool available at their new center to doctors everywhere. They have teamed up with a UCSF lab certified by the Centers for Medicare and Medicaid Services to carry out such diagnostic tests. The certification, called Clinical Laboratory Improvements Amendment, or CLIA, accredits the laboratory where tests, such as DeRisi's microarray test, may be carried out on patients' samples without getting FDA approval.

DeRisi and Chiu are conducting a research study of patients with undiagnosed conditions of suspected viral cause so they can have the microarray test validated for viral discovery in their CLIA-certified lab at UCSF. That would allow them to report their findings routinely to clinicians who could use the information to tailor treatment. At this time, all the analyses carried out at the center are for basic research only. The center is funded by Abbott Diagnostics, a division of the pharmaceutical giant Abbott Labs.

DeRisi says he hopes the center will be ready to receive patient samples for clinical diagnosis before the end of the year. Chiu adds that FDA approval for such a microarray-based test is not in sight for at least the next five years.

DeRisi says the cost of getting a diagnosis at a facility such as the UCSF center would be no more than that of single FDA-approved diagnostic test kits that doctors can now purchase. Such tests cost between $200 and $300 a kit. Further, a broad-spectrum, microarray-based test would screen for many more viruses than any one FDA-approved test.

CHAPTER IV

DIAGNOSIS IN CONTROVERSIAL DISORDERS

Editor's Note: This series of feature stories consists of three articles on the role of diagnosis in modern medicine. Traditional and modern methods of diagnosis affect treatment choices for patients and have a big impact on health care delivery and costs. The first story explains the diagnostic challenges to tailoring cancer treatment to patients' genetic makeup. The second story discusses the role of cutting-edge diagnosis in treating infectious diseases, and the third explores the controversy surrounding the diagnosis of fibromyalgia. Together, the stories represent three facets of diagnosis – the challenges, the promise and the conflicts surrounding this essential part of medical practice. This is the third of three stories.

Two years ago, 25-year-old Kerry Brewer, a native of Cary, N.C., was a different woman. A track-and-field athlete, Brewer took pride in her body's ability to morph into a moving machine. Today, she is thin, gaunt and wiry, the veins on her limbs visibly crisscrossing under the skin.

Brewer's life revolves around visits to the doctor. In the past two years, Brewer has visited more than 30 doctors in search of a name for an ailment whose symptoms have ebbed and surged. Her condition remains nameless, but Brewer is convinced it's only a matter of time before she finds a diagnosis.

Brewer's troubles began in the summer of 2006 during a trip to Thailand where she taught English to Thai orphans. While at the orphanage, Brewer came down with a fever, accompanied by a number of purple spots on her thigh. Antibiotics took care of the spots and the fever, which disappeared after a few days. But a rash of symptoms came back to haunt her repeatedly, like a returning ghost.

For the next two years, Brewer suffered bouts of fatigue, fogginess and widespread pain of mysterious origin – a combination of nebulous symptoms that defied diagnosis and failed to reveal an underlying pathology despite visits to dozens of doctors. The symptoms upended Brewer's life. She declined to enroll in a graduate program in Southeast Asian studies at the University of Michigan. Instead, she spent more than six months at home trying to nurse herself to health. She now attends graduate school in public health at the University of North Carolina at Chapel Hill.

For 15 years before her trip to Thailand, Brewer had been a star athlete in cross-country, track and soccer. As a senior at Cary High School, she was captain of the school teams for all three sports, was elected the school's best female athlete in 2002, and was voted the most valuable person on her school's cross-country, track and soccer teams the same year. As an undergraduate at the University of North Carolina at Chapel Hill, Brewer joined the track team, won five Atlantic Coast Conference championships for track events and ran in several national championship meets. In the fall of 2007, five years after graduating from college, Brewer could barely get up from bed, let alone run.

When she returned from Thailand in September 2006, Brewer visited her primary care physician, Dr. James Womble in Cary, N.C., who ordered a number of diagnostic

tests, looking for viral and bacterial infections. When the tests revealed nothing, Womble sent Brewer to an infectious diseases clinic in Raleigh, N.C., where a specialist ran a different battery of tests for rare, tropical infections, such as yellow fever, dengue, Japanese encephalitis, shingles, scabies and Whipple's disease. "The problem with both of those appointments was that I appeared to be very sick, and I felt awful. But when they would examine me, there wasn't anything wrong, other than the fact that I was saying I felt sick," Brewer says.

In the following months, Brewer was tested for an array of problems – nutritional deficiencies, allergies, gastrointestinal afflictions, muscular inflammation, ear, nose and throat infections and neurological disorders. Pinprick tests for food and environmental allergies drew blanks. Balance tests for equilibrium hit dead ends. Endoscopy of her swallowing tube and stomach showed nothing amiss. Magnetic resonance imaging scans that mapped brain activity picked up nothing of significance. The mystery of the cause of her illness lingered while her quest for a solution intensified.

Brewer is not alone in her plight. Countless patients have grappled with symptoms that defy diagnosis. No definitive statistics exist on the number of patients seeking a diagnosis for mystery illnesses, but a study by the National Institutes of Health's Genetic and Rare Disease Information Center, or GARD, found that 6.6 percent of inquiries to the center between 2005 and 2008 were related to undiagnosed conditions. Further, a 2002 GARD study found that about 50 percent of patients seeking a diagnosis got one in less than a year; about 30 percent got a diagnosis between one and five years; and 15 percent did not receive a diagnosis for at least five years. Furthermore, getting a

diagnosis does not mean that a patient's problem has been correctly identified. The diagnosis could be wrong.

To address the needs of such patients, the National Institutes of Health in Bethesda, Md., opened in May 2008 a center that brings together 25 experts from different medical disciplines under the aegis of the Undiagnosed Diseases Program. With an annual funding of $280,000, program administrators say they want to help patients find diagnoses and treatments for rare conditions that the medical community has given up on. They also want to develop new diagnostic algorithms. To be admitted to the program, a patient must be nominated by a physician willing to make a convincing case for the patient's need for a diagnosis.

Marianne Genetti, president of the Florida-based nonprofit In Need of Diagnosis, says the Undiagnosed Diseases Program is a last-ditch recourse for many people who have almost lost hope. "One of things we want to do is to give these people a voice, an identity. 'Undiagnosed' is a diagnosis. We also want to bring about changes in the medical profession to make it easier not just for those people with rare disorders to get a diagnosis but for everybody to get diagnosed," Genetti says. Genetti, 71, has grappled with a nameless condition for more than 50 years, one characterized by fatigue, diffuse pain and a sporadic inability to move the muscles of her legs. "If there was a fire in my house, I could not get up from the couch to leave. I'd go limp," she says.

Diagnosis has eluded Genetti despite multiple visits to many specialists at the Mayo Clinic in Jacksonville, Fla. Along the way, however, doctors have given her

condition labels like “fibromyalgia,” “chronic fatigue syndrome” and “chemical sensitivity.”

Although they failed to provide a diagnosis, Brewer’s physicians suggested that she might have chronic fatigue syndrome or fibromyalgia, conditions whose existence is hotly debated because of uncertainty about the underlying pathologies.

Fibromyalgia patients suffer widespread pain, fogginess and fatigue, among other symptoms. The disease affects about 10 million Americans, as estimated by doctors treating the disease and by advocacy groups supporting patients. Symptoms of fibromyalgia do not respond to traditional painkillers, and patients generally do not get better with time. The Food and Drug Administration has approved Pfizer’s drug Lyrica and Eli Lilly’s drug Cymbalta for the treatment of fibromyalgia.

Dr. Dan Clauw, a professor of medicine at the University of Michigan, has consulted about fibromyalgia for Pfizer and for other drug companies. He says the clinical criteria for diagnosing fibromyalgia are not clear-cut. In 1990, the American College of Rheumatology put forth criteria for labeling patients with fibromyalgia. These criteria were originally intended to target individuals for research studies of fibromyalgia and not as clinical diagnostic criteria. These criteria include a history of widespread pain for at least three months and pain in 11 of 18 body spots. Despite the limited purpose of the diagnostic markers, many doctors have been using the criteria to establish a diagnosis.

“These people have the symptoms that they say they have. You can go back in the medical literature for millennia and find people that have the exact same symptoms,” Clauw says.

But several physicians refute the existence of the disease, suggesting that drug companies and doctors use the diagnosis of fibromyalgia to medically treat a condition that might be better managed by psychotherapy or by cognitive behavioral therapy. In his book *Worried Sick*, Dr. Nortin Hadler, a rheumatologist and expert on musculoskeletal disorders at the University of North Carolina at Chapel Hill, argues that diagnosing patients with fibromyalgia might worsen their condition. He says the diagnosis sometimes cements patients’ mistaken belief that their perception of pain is an indication of an underlying pathology, and that assumption can lead to unwarranted treatment. “[The patients’] narrative is laced with the clinical heuristics they have learned, which they can recite with objectivity that approaches the dispassionate,” he writes.

Clauw disagrees. “There have been different studies that have looked at what happens after you give someone the diagnosis of fibromyalgia, and they’ve all shown that [the diagnosis] decreases the health care utilization because people stop going to all these subspecialists and getting all these diagnostic tests to find out what’s wrong with them,” he says.

Dr. Frederick Wolfe, director of the National Databank for Rheumatic Diseases, was among the first physicians to put forth the diagnostic criteria for fibromyalgia. Wolfe now concedes that the existence of the disease is debatable, arguing that some doctors interpreted painful spots—called tender points—as a diagnostic sign for fibromyalgia. He

says the tender points might be the result of stress. Further, he says, physicians vary greatly in their ability to detect tender points, rendering the diagnostic criterion shaky.

Clauw says stress and depression may accompany fibromyalgia in about 40 percent of patients, but they are unlikely to be the causes of the symptoms. “Psychotherapy might help a very small subset of fibromyalgia patients in whom the symptoms are driven by psychological and emotional factors, but there are tons of fibromyalgia patients who are psychologically normal. There’s a strong underlying neurobiological basis to pain sensitivity, and that seems to be why these people have their symptoms,” he says.

Wolfe says the disorder is a specific kind of misery. “This isn’t just ordinary misery. It’s an awful lot of misery. In most instances, I don’t agree that the diagnosis of fibromyalgia represents an attempt to medicalize misery,” Wolfe says. But he agrees that using medication to treat something that might not be treatable can worsen the patient’s condition and perpetuate the disorder, a notion some scientists have termed “medicalization of psychosocial problems.”

Many fibromyalgia patients receive drugs that produce more side effects than relief. “The rule in medicine is to do as little as possible and as much as is necessary. Fibromyalgia as a concept has not been useful to society,” he adds. Wolfe suggests that the symptoms that fibromyalgia patients suffer are real, but labeling those symptoms as a disorder with the goal of treating the disorder with medication is debatable.

Clauw considers that viewpoint escapist. “There are a lot of clinicians who are uncomfortable with fibromyalgia patients because we are always uncomfortable when we can’t make people better or when we don’t understand what’s going on in their bodies. They’re transferring their discomfort in trying to blame the patient. These people are really debilitated. They’re not making it up,” he says.

Wolfe says physicians who believe in fibromyalgia as a real disease cite specific abnormalities in the central nervous system as the underpinning of the disorder. “And that’s where one has a problem because there isn’t any good evidence of causality,” he says.

Clauw suggests that such a claim is unfounded. “These suppositions fall apart when you look at the scientific data. [The detractors] rely on their eminence, not on the evidence. Saying that this is the medical [treatment] of misery or the pharmaceutical companies mongering pills is overly simplistic and downright wrong,” he says.

Brewer remembers a turning point in the course of her illness as an unpleasant meeting with her physician Womble. She recalled, “He brought me into his office, and said, ‘Kerry, I need to be honest with you. There’s nothing wrong with you, and I suggest that you see a psychiatrist. It seems like mostly you’ve just worked yourself up into such a tizzy about this whole thing. It’s just psychiatric.’”

The pronouncement took Brewer by surprise. “I just couldn’t believe that this person who had known me for years was *accusing* me of creating a physical disorder through my mind. He was saying *I was causing it myself*,” she says.

Brewer says Womble suggested that she was imagining the illness to escape from her possibly unhappy life situation or to malinger. “Why would I want to do that? I worked very hard to qualify for the world championship. I had a full scholarship to start grad school. Why wouldn’t I want to do those things? Why would I create an illness to back out of that? My family was upset with him. We all stopped going to see him,” she adds.

Womble explains: “Often, the worry and anxiety about not having a diagnosis can produce physical symptoms. Those can be confusing and can make it more difficult to make a diagnosis sometimes.” He adds that once a physician has ruled out an organic cause for the symptoms, it’s reasonable to reassure the patient “that they don’t have anything of a serious nature.”

In October 2007, Brewer found Dr. Alan Spanos, a pain specialist at Blue Ridge Clinical Associates in Chapel Hill, N.C. “He is exactly what I had been looking for, someone who’s unwilling to give up,” Brewer says.

Spanos, a British doctor who has lived in the U.S. since 1979, says an infection that cannot be diagnosed using laboratory tests could be the cause of Brewer’s condition. “My official diagnosis was to describe the condition and be open-minded about what it might turn out to be,” Spanos says. “We have examples of infectious diseases which sit around for a long time, making us all scratch our heads until we finally are able to virtually see the germ under the microscope.”

Spanos suggested that Brewer take a mix of drugs, some in series, others in concert: beta-blockers for her increased heart-beat rate; strong anti-emetics—commonly used by cancer patients—to suppress her nausea; antibiotics to quell any infectious agents lurking in her body; pain medication for her aching muscles; medication commonly given to geriatric patients to retain nutrients in the blood longer than usual; and energy boosters prescribed for patients of narcolepsy and attention deficit hyperactivity disorder. The regimen worked for a while before Brewer's health took another nosedive.

Brewer's symptoms recurred unabated throughout the winter of 2007, and as a last-ditch effort, Spanos suggested that she take an antibiotic cocktail daily. The drugs—doxycyclin and minocycline—alleviated most of her symptoms and kept her functional. "There's no real reason that I'm taking it other than the fact that it works," Brewer says.

Spanos says he was outraged at Womble's suggestion that Brewer see a psychiatrist for her troubles. "In contemporary American medicine, there's an unfortunate tendency to say that it doesn't matter what the patient is telling me, it doesn't matter how they look, it doesn't matter what they find on examination – if the tests are all negative, then they're not really ill. This is obvious baloney and would be treated as baloney in almost every other country in the world," he says.

"Doctors would much rather make a diagnosis—even the demeaning and potentially false one of a psychiatric condition—than admit to the patient and to themselves that this is an unusual illness. We don't know what it is," Spanos says. "There are quite a few folks out there with illnesses which are not in our textbooks. Not only are

they not in our textbooks, but we don't even know what chapter of the textbook they should go in."

Brewer continues to search for a definitive diagnosis amid the welter of names that hover around her condition: fibromyalgia, chronic fatigue syndrome, a mysterious infection and metabolic deficiency. Out of desperation, she has accepted that her quest to find a name and cause of her condition might continue indefinitely.

On the other hand, she keeps looking for answers. "I still have hope that there is this simple explanation and this simple drug that I could take that will make it all better. I hope that a lot less than I used to, but I still hold on to that hope," she says.

CHAPTER V

FUTURE PERSPECTIVES

The three stories in this thesis provide insights into the role of diagnosis in personalized cancer treatment, in the treatment of infectious diseases and in the plight of patients suffering from controversial disorders. But they also raise a number of questions for future exploration.

Molecular diagnosis has just begun to reshape doctors' approach to cancer therapy, but there are several roadblocks along the way, some of which the story on cancer biomarkers addresses. Other concerns not broached in the story could form the bases for future stories on personalized cancer treatment. One concern relates to the challenges to translating basic research for biomarker discovery, which happens in laboratory settings, into clinical trials for biomarker validation, which happens in hospital settings. Basic researchers working to find biomarkers for cancer are sometimes unaware of how patients' samples were collected, stored and compared in clinical settings. In the past, that gap in knowledge has led to unwarranted assumptions and, therefore, unreliable biomarkers. Another concern relates to the Herculean task of determining the uniqueness of individuals' cancer. Such an endeavor would ideally involve tens of thousands of patients and millions of dollars. Attempts to personalize cancer therapy are doomed to fail without this knowledge, and cancer researchers are now trying to chart the panoply of

genetic abnormalities found in certain types of cancer with the goal of determining which of those changes could trigger cancer.

Using microarrays, scientists have made inroads into the discovery of novel viruses and of emerging infections, as the second story in the series shows. But it's hard to get approval from the Food and Drug Administration for the use of microarrays in the development of clinical diagnostic tests, partly because the FDA is unsure of how to go about setting up benchmarks for such approval. One ongoing effort by the FDA—the Microarray Quality Control Project—addresses some of those problems and is aimed at publishing a set of guidelines later this year for the use of microarrays in diagnostics. This is an emerging field of research with many unanswered questions – and a gold mine of story ideas for future popular science stories.

The story on controversial diseases, such as fibromyalgia, highlights the patient's perspective while setting up the debate between the proponents of the biological and psychosocial causes of fibromyalgia. Many intriguing research questions relate to such conditions, which would lend themselves to popular storytelling: How does the processing of pain by the human body make some individuals sensitive to stimuli that are not normally painful? Does the interplay between the nervous system and hormones produce some of the symptoms associated with chronic pain? Can exercise improve the body's ability to handle stress and reduce pain perception in individuals with fibromyalgia? Could some individuals have a genetic predisposition to fibromyalgia? Scientists are beginning to answer some of these questions. For others, the answers seem obscure.

Guidance to reporters covering medical stories

Medical stories tend to present unique challenges to reporters because of the often complex nature of the underlying science and the dense, scholarly language of academic medical journals, which regularly serve as source materials for stories. To ensure that readers understand the importance, implications, nuances and limitations of medical advances, reporters could follow several steps to make their arguments convincing and their stories readable. Here, I have listed six simple strategies that could help medical journalists make their prose lucid to a lay audience:

- Metaphors and analogies can help reporters render abstract scientific phenomena concrete to the lay reader. Choosing metaphors wisely is no mean feat; a well-chosen metaphor should help a reader understand a concept and its intricate details. Reporters could also ask the scientific expert to come up with literary devices and then attribute the usage to the source.

- Reporters should avoid using jargon in popular stories. Instead, they should explain concepts in plain English.

- Science writers can avoid confusion in their writing by backing into explanations. This time-tested strategy in science writing consists of explaining scientific concepts before labeling them.

- One way to make text readable, especially while dealing with complicated subject matter, is to use a combination of techniques for spare, straightforward writing: using short, declarative sentences; limiting the number of ideas per sentence to

one; choosing five-cent words over fancy, ten-dollar alternatives; culling adverbs and adjectives; and avoiding passive voice whenever possible.

- The power of narrative structure in helping readers wrap their minds around complex ideas can never be stressed enough. Narrative is probably the journalist's single most important trick in the toolbox. The AB-BC-CD rule in narrative writing—picking up on the last word of a preceding sentence or graf to begin a new one—helps ensure continuity of expression. Also, transitional phrases can ensure that a story's progression resembles a purposeful flow rather than an aimless wander. Such structural formulae act like chicken-wire in a story, helping the writer herd all the tangential subplots into a multidimensional story.

- Finally, reporters should follow the cardinal rule in science writing: Never write about what you don't understand.

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