No. 09-1156

IN THE

Supreme Court of the United States

MATRIXX INITIATIVES, INC., ET AL.,
Petitioners,

v.

JAMES SIRACUSANO AND NECA-IBEW PENSION FUND,
Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

BRIEF OF *AMICI CURIAE* MEDICAL RESEARCHERS DR. TONIA M. YOUNG-FADOK (MAYO CLINIC), DR. CURT D. FURBERG (WAKE FOREST), DR. ERIC J. TOPOL (SCRIPPS), AND DR. DAVID A. ETZIONI (MAYO CLINIC) IN SUPPORT OF RESPONDENTS URGING AFFIRMANCE

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BRIEF OF *AMICI CURIAE* MEDICAL RESEARCHERS DR. TONIA M. YOUNG-FADOK (MAYO CLINIC), DR. CURT D. FURBERG (WAKE FOREST), DR. ERIC J. TOPOL (SCRIPPS), AND DR. DAVID A. ETZIONI (MAYO CLINIC) IN SUPPORT OF RESPONDENTS URGING AFFIRMANCE

INTEREST OF *AMICI CURIAE*

Amicus Tonia M. Young-Fadok, M.D., MS, FACS, FASCRS, is Professor of Surgery, Mayo Clinic College of Medicine, and Chair, Division of Colon and Rectal Surgery, Mayo Clinic, Arizona. Dr. Young-Fadok is a leading medical researcher in diseases of the colon and rectum, with specific reference to the application of laparoscopic techniques to improve patient outcomes. She has participated in many clinical trials in the field of colon and rectal surgery. She has published over 40 research papers as primary investigator, 59 peer-reviewed articles, 36 book chapters, and numerous other publications. She is an editorial board member of eight medical journals and a reviewer for 17 others. She has made presentations at over 160 medical conferences nationally and internationally.[1]

Amicus Curt D. Furberg, M.D., is Professor of Public Health Sciences and Senior Advisor to the Dean for Health Services Research and Health Policy

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[1] This brief has been filed with the written consent of the parties, which is on file with the Clerk of Court. Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amici* or their counsel, make a monetary contribution to the preparation or submission of this brief.

at Wake Forest University School of Medicine. From 1979 to 1985, he was Chief of the Clinical Trials Branch of the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) in Bethesda, Maryland. In 1986, he was appointed Director, Center for Prevention Research and Biometry, and Head, Section of Prevention Research and Biometry in the Department of Medicine at Wake Forest. From 1989 until 1999, he was Chairman of the Department of Public Health Sciences at Wake Forest. Under Dr. Furberg's leadership, the Center and the Department grew from one to approximately 300 persons. The Department successfully competes for NIH funding and in recent years has ranked nationally as one of the top two departments of its type for NIH funding. Dr. Furberg has more than three decades of expertise and experience in the areas of epidemiology and clinical trial design, conduct, monitoring, interpretation, and reporting. He is a national leader in the field. He has served as Principal Investigator or Scientific Project Officer on a large number of primarily cardiovascular clinical trials, having played a very active role in their design, conduct, monitoring, interpretation, and reporting. These trials documented the efficacy and safety of various interventions and led to improvements in the quality of care for millions of patients with coronary heart disease, heart failure, hypertension, or other vascular conditions. He has served or is currently serving on the Data Safety Monitoring Committees for over 50 clinical trials sponsored by the NIH, various foundations, the pharmaceutical industry, and others, including the Data Safety Monitoring Committees of two ongoing industry-sponsored trials. These committees monitor

the efficacy and safety of treatment and prevention trials in progress and are charged with recommending early trial termination, if efficacy is clearly documented or if harmful effects outweigh the benefits. Thus, Dr. Furberg is experienced in the generally accepted approaches to weighing favorable and unfavorable effects of interventions, primarily medications. He is frequently consulted on clinical trial issues by colleagues at academic institutions and has conducted trials sponsored by pharmaceutical companies. He consulted for Wyeth as an expert regarding the diet-drug combination fenfluramine-phenteramine (so-called "fen-phen") in determining the magnitude of the adverse effects associated with its use. He has also been an advisor to the World Health Organization (WHO) and is currently conducting a WHO-sponsored study in Sri Lanka as part of a program directed at non-communicable diseases in low- and middle-income countries.

Amicus Eric J. Topol, M.D., is the Director of the Scripps Translational Science Institute, a National Institutes of Health-funded program of the Clinical and Translational Science Award (CTSA) Consortium focused on advancing individualized medicine. He is the Chief Academic Officer of Scripps Health, a Senior Consultant cardiologist practitioner at Scripps Clinic, and Professor of Translational Genomics at The Scripps Research Institute. Prior to coming to Scripps, he served on the faculty of Case Western as a professor in genetics, chaired the Department of Cardiovascular Medicine at Cleveland Clinic for 15 years and raised its status to rank #1 by U.S. News and World Report for 11 consecutive years, and was Founder of the Cleveland Clinic Lerner College of

Medicine. His work in the genomics of heart attack has led to discovery of key genes recognized by the American Heart Association twice as top 10 research advances. As a leader in clinical trials of novel therapeutics, he administered recombinant t-PA to the first patient in 1984 and pioneered and led the clinical development of clopidogrel (Plavix), bivalirudin (Angiomax), and abciximab (ReoPro). He was the first physician to publish safety concerns on the cardiovascular risk of Vioxx. He has over 1,000 original peer-reviewed publications and has edited over 30 books, including the Textbook of Interventional Cardiology (5th ed.) and the Textbook of Cardiovascular Medicine (3rd ed.). He has been a medical innovator in wireless medicine, including wireless ECG telemetry, vital signs, remote monitoring for heart failure, and as a Founder and Vice-Chairman of the West Wireless Health Institute. Dr. Topol has been elected to the Institute of Medicine of the National Academy of Sciences and the American Association of Physicians, and has been recognized by the Institute of Scientific Information to be in the top 10 cited biomedical researchers in medicine in the past decade.

Amicus David A. Etzioni, M.D., MSHS, FACS, is Associate Professor of Surgery, Mayo Clinic College of Medicine, and Senior Associate Consultant, Division of Colon and Rectal Surgery, Mayo Clinic, Arizona. Dr. Etzioni has extensive expertise in health services research, the study of quality as it pertains to health care delivery. In his career as a health services researcher, he has published in a wide range of topics, including critical reviews of the status of medical evidence. His experience in analyzing and

synthesizing medical knowledge will be important in giving context to the discussions of the importance of different types of scientific evidence.

Amici's expertise is directly relevant to the question presented in this case. They are very familiar with different methods by which medical information is gathered, including case reports and case series. They are well acquainted with the means by which the strength of scientific evidence is assessed and the role of case reports in prompting scientific alerts and further investigation. They can therefore provide this Court with an important perspective regarding the type and quantum of evidence by which medical researchers and professionals routinely take action and make decisions.

SUMMARY OF ARGUMENT

Petitioners in this case contend that Adverse Event Reports (AERs) are not material information unless they reveal a statistically significant increased risk of harm from product use. Yet medical researchers and professionals do not follow such an approach. They do not ignore relevant medical data, including reports of adverse events, or wait until the information rises to the level of statistical significance. They do not restrict the data they consider to the results of randomized clinical trials. To the contrary – medical professionals frequently act on the basis of case reports and other information that may not meet the standard of statistical significance.

Randomized trials have important ethical, practical, and statistical limitations. Although side

effects are tolerated as part of efficacy studies, trials usually are not conducted merely to confirm the presence of serious side effects. Randomized trials are designed to evaluate desired outcomes, while monitoring for adverse outcomes. Thus, medical researchers would not perform a randomized controlled trial simply to examine whether the specific outcome of anosmia is linked to the intranasal gluconate gel used in Zicam products. It would be ethically unjustifiable to undertake a randomized trial solely to evaluate a complication such as anosmia.

Further, clinical trials generally lack the statistical "power" to detect rare side effects. The number of participants in randomized controlled trials is usually calculated to demonstrate statistical significance in terms of a chosen outcome, such as efficacy, and is not designed to reveal rare serious adverse effects.

Because of the limitations of randomized trials, the medical community also considers case reports and case series to be important sources of material information. Case reports and case series have played key roles in many decisions by the medical community to investigate apparent risks, modify procedures or guidelines, and take other kinds of action. Examples include the dangers of Thalidomide, the risks of oral contraceptives (particularly deep vein thrombosis and subsequent pulmonary embolus), the link between Reye's Syndrome and aspirin, the side effects of rofecoxib (Vioxx), the identification of Acquired Immunodeficiency Syndrome, commonly known as AIDS, and

complications arising from laparoscopic surgery for colon cancer.

With respect to pharmaceuticals, the Food and Drug Administration (FDA) has recognized that case reports and case series can play important roles in serving as "safety signals" and raising concerns about an excess of adverse events compared to what would be expected to be associated with a product's use. Notably, such reports need not rise to a statistically significant level in order to trigger action.

In fact, case studies have already formed a basis for action on the part of medical professionals with respect to the intranasal gluconate gel in Zicam products. Based on the information available in 2003, medical professionals had a reasonable basis for undertaking further investigation with respect to anosmia.

Statistical significance simply is not the "be-all" and "end-all" for the medical profession in identifying medical risks and formulating appropriate responses. Accordingly, statistical significance should not be used as a rigid, bright-line standard for defining the materiality requirement for reasonable investors in the context of medical risks.

The judgment should be affirmed.

ARGUMENT

A. There Are Ethical, Financial, and Scientific Limits on Randomized Trials.

Contemporary medical professionals practice evidence-based medicine, *i.e.*, "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual

patients."[2] Medical professionals must integrate individual clinical expertise with the best available external clinical evidence from systematic research. In combining this range of data from various sources, medical professionals do not restrict their attention to information that meets a standard of statistical significance.

Rather, medical professionals rely on their personal experience, proficiency, and judgment developed through clinical practice. They also consult the best available external evidence, including clinically relevant research, both from basic sciences and from patient-centered clinical research into the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. Good doctors must use both individual clinical expertise and the best available external evidence, because neither alone is sufficient.[3] Clinical expertise is necessary to determine if external evidence is applicable to or appropriate for an individual patient. Consulting current best evidence is necessary to prevent practice becoming out of date.

Ever since the concept of randomization was first introduced by Fisher in agricultural research in 1926, randomized clinical trials (prospective studies comparing the effect and value of interventions against a control) or meta-analyses (the systematic reviews of several randomized trials) have often been treated as the "gold standard" for judging whether a

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[2] Sackett DL, Rosenberg WMC, Muir Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. Brit Med J (1996) 312:71-72.

[3] *Id.*

treatment does more harm than good.[4] In a randomized trial, a participant is randomly assigned to either the "study" group (which receives the particular intervention at issue) or the "control" group (which does not receive the intervention). The ideal trial is one that is randomized and double-blinded – neither the participant nor the investigator knows if the participant is in the study group or the control group.

However, evidence-based medicine is not restricted to the results of randomized trials or meta-analyses. Indeed, the practical reality is that many questions about medical care and treatment do not require randomized trials or cannot wait for trials to be conceived and conducted. And if there is no evidence from a randomized trial that addresses a patient's situation, it is important to look for the next best external evidence. As a leading pharmaceutical manufacturer explains on its website, "[r]esults from clinical studies, spontaneous reports, epidemiology studies, and, where relevant, preclinical datasets, should all be evaluated for their potential to address the particular safety question raised, taking into account the unique strengths and limitations of the study designs and data collection methods used."[5]

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[4] Friedman LM, Furberg CD, DeMets DL. "Fundamentals of Clinical Trials" (4th ed. 2010, Springer-Verlag, New York), p. 1.

[5] http://media.pfizer.com/files/health/medicine_safety/2-5_How_is_Epidemiology_Used.pdf (last accessed November 4, 2010).

In some situations, randomized trials are precluded on ethical grounds – for example, where researchers have a reasonable basis for believing that members of the study group or control group will experience serious harm.[6] To be sure, there never has been, and never will be, a randomized trial of the benefits of parachutes for skydivers. Similarly, researchers typically do not conduct randomized trials if they already have a basis for believing that a particular intervention would have serious negative side effects that outweigh any potential positive gain from the intervention.

Moreover, clinical trials generally are not undertaken merely to confirm the existence of already suspected serious side effects. To be sure, physicians often observe a side effect when investigating an intervention's efficacy in treating a disease, but it is an entirely different matter to expose study subjects to serious side effect risks simply to confirm that those risks exist. Medical ethics would severely limit the types of investigations that would be permissible in such circumstances.

In this case, there would be serious ethical questions about a clinical trial of the intranasal

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[6] AMA Code of Medical Ethics, Opinion 2.07, subpart (2) ("In conducting clinical investigation, the investigator should demonstrate the same concern and caution for the welfare, safety, and comfort of the person involved as is required of a physician who is furnishing medical care to a patient independent of any clinical investigation."); *id.* at subpart (5)(a) ("Adequate safeguards must be provided for the welfare, safety, and comfort of the subject. It is fundamental social policy that the advancement of scientific knowledge must always be secondary to primary concern for the individual.").

gluconate gel used in Zicam products, given what doctors already know about the serious side effect risk of anosmia. Because of the obvious ethical concerns, researchers would be highly unlikely to conduct a randomized study merely to make sure that subjects really will lose their sense of smell.

Further, randomized trials typically lack the "power" to detect adverse effects that occur only rarely. In statistical terms, the ability of a study to detect a "real" effect is often referred to as the "power" of a study, or the probability that the study will lead to the identification of a true effect, as opposed to being the result of chance.[7] Statistical power is a function of the size of the treatment effect, the number of study participants, and the duration of the study. Trials are generally designed to examine a single goal, such as efficacy, or a very limited number of endpoints that are clearly stated in advance. Efficacy studies, which test an endpoint occurring with high frequency in smaller sample sizes, are simply not powered to detect rare adverse events. Hence, unless the control and study groups are very large and are followed for a substantial period of time (both of which greatly increase the cost of the investigation), the trial is unlikely to identify adverse effects that occur relatively rarely in the population.

In the case of the intranasal gluconate gel used in Zicam products, several randomized trials actually have been performed. Two randomized trials have reported that intranasal zinc is ineffective in preventing or reducing the duration of the common

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[7] Piantadosi, S. Clinical Trials: A Methodologic Perspective (1997), p. 528.

cold.[8] In the study by Belongia et al., 81 patients were randomized to receive zinc gel and 79 to placebo. Review of adverse events did not include a report of anosmia, but the study would have been underpowered to demonstrate such a rare side effect. A study by Hirt et al. did show a shorter duration of cold symptoms, and did not report anosmia, but only 108 and 105 patients were assigned to the study and control groups, respectively.[9] And a study by Mossad involved only 78 patients total, with 40 in the study group and 38 in the placebo.[10] In other words, none of the trials could have been expected to detect anosmia as a side effect.

Moreover, to the extent that an adverse event occurs in a clinical trial designed to assess the efficacy of treatment, it is unlikely that there would be a sufficient number of adverse events to achieve statistical significance at the 95% confidence level. However, lack of statistical significance should not be mistaken either for an absence of increased risk of harm or for confirmation that a drug is safe. As one researcher noted in the context of Bextra

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[8] Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. Am J Med (2001) 111(2):103-08; Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. Clin Infectious Dis (2001) 33(11):1865-70.

[9] Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. Ear, Nose & Throat J (2000) 79(10):778-80, 782.

[10] Mossad, SB. Effect of zincum gluconicum nasal gel on the common cold in otherwise healthy adults. QJ Med (2003) 96:35-43.

(valdecoxib), a non-steroidal anti-inflammatory drug (NSAID) removed from the market in 2005, due to concerns about possible increased risk of heart attack and stroke:

> The . . . argument that the event rate for cardiovascular thrombotic events is not statistically significant different from placebo is technically correct but misses the point that statistical significance is not an appropriate threshold for the evaluation of clinical safety data: theoretically, one event may be of clinical significance.[11]

The Institute of Medicine of the National Academies reports that pre-market trials generally involve no more than 600 to 3,000 patients and that such trials cannot reveal the safety problems that may emerge only after long-term, large-scale use:

> Preapproval trials typically are too small to detect even significant safety problems if they are rare. An adverse event (even a serious one) that occurs in less than one in 1,000 patients cannot be reliably detected except in the largest premarket trials but can pose a serious public health problem when hundreds of thousands or millions of people use the drug.[12]

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[11] Lyons, et al. Valdecoxib Second Article 31 Procedure Rapporteur's and Co-rapporteur's Joint Assessment Report (2005 Jan 26).

[12] Institute of Medicine. The Future of Drug Safety: Promoting and Protecting the Health of the Public (Alina Baciu, Kathleen Stratton & Shelia P. Burke eds., 2007), pp. 37-38

As one major drug company – Pfizer – acknowledges on its website, "preapproval studies are rarely large enough to detect small differences in the risk of common adverse events or to reliably estimate the risk of rare events."[13]

A well-publicized contemporary example of the limited power of pre-approval studies is Vioxx, which has now been withdrawn over safety concerns. Rofecoxib was approved by the FDA on May 20, 1999, and was marketed by Merck & Co. under the brand name Vioxx. Indications for prescription were treatment of osteoarthritis, acute pain conditions, and dysmenorrhoea. Rofecoxib was widely prescribed by physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, it is estimated that over 80 million people were prescribed rofecoxib prior to its 2004 withdrawal, over concerns about increased risk of vascular disorders such as heart attack and stroke associated with long-term, high-dosage use.[14]

The decision to withdraw the drug from the market was based on data from a study of rofecoxib in the prevention of colonic polyps (adenomas) (APPROVe) trial. In this study 2,586 patients were

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(citations omitted).

[13] http://media.pfizer.com/files/health/medicine_safety/2-5_How_is_Epidemiology_Used.pdf (last accessed November 4, 2010).

[14] Merck News Release dated September 30, 2004, *available at* http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf (last accessed November 4, 2010).

randomized to rofecoxib (25 mg/day) or placebo with a planned follow-up of three years.[15] Tellingly, the decision to withdraw the medication from the market (September 30, 2004) was made prior to publication of the article in the New England Journal of Medicine (NEJM) (March 17, 2005) and reflects the behind-the-scenes reporting of results by Merck to the FDA and the NEJM. Safety monitoring of adverse events indicated a significant excess difference in the incidence of thrombotic cardiovascular events (such as myocardial infarction and stroke) in the study group that received rofecoxib. Other studies reported similar risks.[16]

These studies are illustrative of the difficulty in eliciting the risk of rare but serious outcomes during randomized controlled trials. Randomized trials are "powered" to show statistically significant common outcomes, not rare complications. Relatively rare side effects may not be noted and reported until the medication becomes available to a much larger population of patients. The Vioxx example involved an extremely well-funded trial of nearly 2,600 patients, and even then there was controversy regarding whether the risk of cardiac events was

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[15] Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med (2005) 352(11):1092-102. Epub 2005 Feb 15.

[16] Kerr DJ, Dunn JA, Langman MJ, Smith JL, Midgley RS, Stanley A, Stokes JC, Julier P, Iveson C, Duvvuri R, McConkey CC. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med (2007) 357(4):360-69.

realized at the time of the first data analysis.

For all these reasons, statistically significant evidence from randomized trials is not the sole source of material information for medical professionals. Nor is statistical significance equivalent to the legal burden of proof.[17]

B. Case Reports and Case Series Represent Important Sources of Information for Medicine and Epidemiology.

In view of the limits of randomized trials, medical researchers and professionals rely on other methods of determining the value, or harm, of interventions. These methods fall within the broader field of epidemiology, which can be defined as the study of the distribution and determinants of disease frequency in human populations. Epidemiology is based on the fundamental assumptions that human disease does not occur at random and that human disease has causal and preventive factors that can be identified through systematic investigation.[18]

Epidemiological principles and methods are concerned with *frequency*, *distribution*, and *determinants* of disease. Measuring disease *frequency* involves quantifying disease occurrence. Determining the *distribution* of disease involves investigating who is getting the disease within a population and perhaps where and when. These factors are important in describing patterns of

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[17] Green, MD, Freedman, DM, Gordis, L. Reference Guide on Epidemiology (2000, Federal Judicial Center), p. 358 n.67.

[18] Hennekens CH, Buring JE. In Epidemiology in Medicine (1987, Little, Brown and Company, Boston/Toronto), p. 3.

disease and formulating a hypothesis regarding possible causal or preventive factors. The third component of epidemiology, the *determinants* of disease, is related to the first two, because data regarding frequency and distribution of disease are required to test an epidemiologic hypothesis.

Epidemiological researchers use many types of studies. The basic design strategies can be broadly categorized into two types, depending on whether the study describes the distributions of disease or analyzes its determinants.[19] Descriptive epidemiology investigates the distribution of disease, including, for example, the populations or subgroups that do (or do not) develop a particular disease or symptom. Analytic epidemiology looks at the determinants of disease by testing hypotheses formulated from descriptive studies.

Descriptive studies are thus important in bringing to light new ideas regarding potential cause-and-effect associations and formulating hypotheses for further evaluation. Descriptive studies include correlational studies, case reports and case series, and cross-sectional surveys.

A correlational study uses data from large populations to compare the frequency of a specific disease between different populations during the same time period or the same population during different time periods.[20] For example, researchers have found that the risk of developing colon cancer is associated with various dietary components. When

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[19] *Id.*

[20] *Id.*

scientists compare the national per capita consumption of meat with rates of colon cancer in women from multiple countries, they find a positive correlation between per capita national meat consumption and development of colon cancer. This approach, however, offers only the view from 100,000 feet. Because correlational studies focus on large populations, it is impossible to determine if the women who develop colon cancer in each country are those with the highest intake of meat. The only conclusion that can be drawn is that populations with the highest intake have the highest rate of colon cancer. Meat may not be the causative factor, but instead a "marker" for other potentially causative traits, such as grilled food, obesity, high caloric intake, low fiber intake, lack of exercise, and so on. Such correlational data can raise hypotheses that require further analytic testing.

The case report is the most basic type of descriptive study and involves a detailed report by one or more experienced clinicians of a case considered rare and thus worthy of attention. These reports provide details of patients presenting symptoms and signs that have not previously been reported, or only rarely reported, in the medical academic literature. Case reports play key roles in medical treatment. When physicians encounter a case or constellation of symptoms and findings they have not seen before, nor even heard described, they look to case reports and small case series for information about how to manage such unusual conditions. These are the types of cases that are not addressed by textbooks or conventional medical training. They are simply too rare.

Case series are equally important to medical professionals. A case series alerts the medical community that a physician, or team of collaborating physicians, has identified a constellation of symptoms or signs, not previously reported, in more than one patient. Case reports and case series are reported to a larger audience in various ways, including local presentation to an institutional division or department meeting that confirms the rarity of the condition, or formal presentation at a regional or national medical society meeting in the form of a poster, video, or podium presentation, that may garner attention or inspire further investigation, or publication in a medical journal.

Medical professionals do not limit their focus to statistically significant data in published studies. Indeed, they do not limit their concern to published data at all. Many notable case reports and case series are never published in medical journals, often due to the pressures that affect publication, even though many journals have acknowledged that case reports are the most widely read pieces among their audience. However, medical journals have a strong incentive to carry articles that will in turn be cited by other peer-reviewed articles, because the number of such citations forms the basis of a journal's significance (or impact factor). Thus, a medical journal has an interest in carrying articles that describe common conditions, because such articles are more likely to be cited elsewhere and thereby increase the journal's impact factors. Case reports, even though they are the favorites of the readership, have little impact factor, because they tend to be rarely cited in light of the fact that, by definition, the

conditions they describe are rare. Some journals have even excluded case reports and case series altogether. Such exclusion does not diminish their ability to effect investigation and change, but it does mean that focusing on published medical literature can create a false impression of the kind of information that forms a basis for action by medical researchers and professionals.

Medical journals and medical societies that publish reviews and guidelines will frequently ascribe "levels of evidence" to conclusions and recommendations. There is no single grading system. One system has been developed by the American Thoracic Society, which convened the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) working group to conduct a review of existing grading systems and develop a system for grading the quality of evidence and strength of recommendations of clinical practice guidelines (CPG).[21] Other societies have adapted this system, including the American Society of Colon and Rectal Surgeons. Yet other groups, such as the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), use a more simplified approach.[22]

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[21] Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G. ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respiratory & Critical Care Med (2006) 174(5):605, 612.

[22] Wexner SD, et al. A Consensus document on bowel preparation before colonoscopy: prepared by a task force from

All of these scoring systems recognize an important role for observational studies, case reports, and case series, particularly where no randomized controlled trials are available.

C. Case Reports or Case Series Have Formed the Basis for Action in Many Well-Known Instances.

The FDA has recognized that case reports and case series can play important roles in serving as "safety signals" and raising concerns about an excess of adverse events compared to what would be expected to be associated with a given product's use.[23] Such reports need not rise to a statistically significant level in order to trigger FDA action. In fact, the FDA states that "[i]t is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use."[24] Pfizer similarly observes that "a safety signal [is] reported information on a possible causal relationship between an adverse event and a

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the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal Surgeons (SAGES). Dis Colon & Rectum (2006) 49:792-809; Perry WP, et al. Practice parameters for the management of anal fissures (3rd revision). Dis Colon & Rectum (2010) 53:1110-15.

[23] U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005 Mar), p. 4, *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf.

[24] *Id.*

drug, the relationship being unknown or incompletely documented previously. When a safety signal is identified, further investigation is generally warranted to determine whether an actual connection exists."[25] FDA regulations do not require a statistically significant association between a drug and a given effect to warrant a label change such as a precaution or warning. *See* 21 C.F.R. § 201.57(e) ("The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.").

Accordingly, case reports and case series have often spurred the medical community to investigate apparent risks, modify procedures or guidelines, and take other kinds of action. For example, the dangers of the drug Thalidomide when administered during pregnancy originally came to light through the publication of a letter in The Lancet, in December 1961, by an Australian gynecologist and obstetrician, noting a large number of birth defects in children of patients who had been prescribed the drug.[26] Thus, a case report was the initial trigger of the public response to the Thalidomide tragedy, which led to substantial regulatory reforms in the United States and elsewhere.

In addition, risks of oral contraceptives were

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[25] http://media.pfizer.com/files/health/medicine_safety/2-4_What_is_a_Safety_Signal.pdf (last accessed November 4, 2010).

[26] William McBride, Letter to the Editor, in The Lancet, 16 Dec 1961.

initially identified through case reports.[27] Physicians now accept that the use of oral contraceptives is associated with an increased risk of deep vein thrombosis (DVT), in which clots form in the deep veins of the legs, and subsequent pulmonary embolus (PE), in which a portion of the clot in the leg detaches and travels back to the lung in the venous system, causing chest pain, shortness of breath, and death, if it blocks the venous return of blood to the heart. Investigation of this phenomenon began in 1961 with a case report of a 40-year-old premenopausal woman who presented with a PE five weeks after starting an oral contraceptive for endometriosis. Because PE was more common in post-menopausal women, the author of the case report hypothesized that the medication may have been instrumental in the development of the clot. Subsequent studies, stimulated by this report, have consistently shown correlation between use of oral contraceptives and risk of DVT and PE. Currently, the manufacturer-informational-insert in every pack of oral contraceptives includes a warning regarding the risk of DVT and PE, and additionally advises against the use of this medication in women who smoke, as further study has indicated this is an additional risk factor for DVT and PE.

Another complication that was identified through initial case reports is Reye's Syndrome, an encephalopathy that develops during the course of varicella (chicken pox) infection in children and typically presents with a distinct constellation of

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[27] Hennekens CH, Buring JE. In Epidemiology in Medicine (1987, Little, Brown and Company, Boston/Toronto), p. 3.

symptoms including nausea, vomiting, headache, excitability, delirium, and combativeness with frequent progression to coma. It can also involve liver dysfunction or failure.[28] The mortality rate of Reye's Syndrome can approach 30%. The syndrome was first described in Australia in 1963, and that same year the Centers for Disease Control (CDC) initiated a registry of cases in the United States.[29] By 1982, over 2,000 cases had been reported.

Case reports and case series played a significant role in the investigation of Reye's Syndrome. As sporadic reports accumulated, they raised suspicion of a link with the use of salicylate (aspirin). This prompted a number of case-control studies in the United States between 1978 and 1989, showing an association between Reye's Syndrome and aspirin.[30]

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[28] Hurwitz ES, Nelson DB, Davis C, Morens D, Schonberger LB. National surveillance for Reye syndrome: a five-year review. Pediatrics (1982 Dec) 70(6):895-900.

[29] Porter JD, Robinson PH, Glasgow JF, Banks JH, Hall SM. Trends in the incidence of Reye's syndrome and the use of aspirin. Arch Dis Child (1990) 65:826-29.

[30] Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicylate use. Pediatrics (1980) 66:859-64; Hallpin TJ, Holtzhauer FJ, Campbell RJ, et al. Reye's syndrome and medication use. JAMA (1982) 248:687-91; Waldman RJ, Hall WN, McGee H, VanAmburg G. Aspirin as a risk factor in Reye's syndrome. JAMA (1982) 247:3089-94; Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study on Reye's syndrome and medications: report of the pilot phase. N Engl J Med (1985) 313:849-57; Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service Study of Reye's syndrome and medications: report of the main study. JAMA (1987) 257:1905-11; Forsyth BW, Horwitz RI, Acampora D, et al. New epidemiologic evidence confirming that bias does not explain the aspirin/Reye's syndrome association. JAMA

Consequently, public health authorities required warning labels to be placed on aspirin products and introduced a public education campaign throughout the United States in 1985, advising against the administration of aspirin to febrile children. Since aspirin use was identified as a major precipitating factor for the development of Reye's Syndrome,[31] this complication has virtually disappeared. In a surveillance study from 1980 through 1997, 1,207 cases were reported; the number of cases peaked in 1980 at 555 and dramatically declined thereafter, after warnings were issued against the use of aspirin in patients with varicella or influenza.[32] From 1987 to 1993, fewer than 36 cases per year were reported; fewer than two cases per year were noted from 1994 to 1997. Currently, Micromedex lists the following as a contraindication to the use of aspirin: "children and teenagers with chickenpox or flu symptoms (risk of Reye's syndrome)." This major change in prescribing practice arose because of the astute reporting of a previously unexpected link between the medication and a severe adverse effect.

One of the most famous medical discoveries to have emerged through case series is Acquired

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(1989) 17:2517-24; Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med (1999) 340(18):1377-82.

[31] Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study on Reye's syndrome and medications: report of the pilot phase. N Engl J Med (1985) 313:849-57.

[32] Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med (1999) 340(18):1377-82.

Immunodeficiency Syndrome, commonly known as AIDS. In 1981, for example, the CDC assimilated the reports of several investigators who reported the diagnosis of *Pneumocystis carinii* pneumonia in five patients at three Los Angeles hospitals in a 6-month period from 1980 to 1981.[33] This was a rare causative organism for pneumonia, previously seen only in immunocompromised, older men and women, such as transplant patients. The common factor was that the five patients were all previously healthy homosexual men. Given the characteristics of the otherwise healthy group, further investigation proceeded and confirmed the diagnosis of this newly described disease. In the absence of the reported case series, the confirmation of the AIDS diagnosis could not have been made in a timely fashion.

Another recent example reveals the importance of case reports and case series in changing clinical practice.[34] The current era of laparoscopic or minimally invasive surgery commenced with the introduction of laparoscopic cholecystectomy (removal of the gallbladder) in 1987 in France[35] and in 1988 in the United States by Reddick and Olsen.[36] This procedure was rapidly accepted by patients and

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[33] Centers for Disease Control. Pneumocystis pneumonia – Los Angeles. MMWR (1981) 30:250.

[34] Young-Fadok TM. Minimally invasive techniques for colorectal cancer. Surg Oncol (1998) 7(3-4):165-73.

[35] Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy: Preliminary report of 36 cases. Ann Surg (1990) 211:60-62.

[36] Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy: A comparison with mini-lap cholecystectomy. Surg Endosc (1989) 3:131-33.

surgeons alike, and this led to the application of minimally invasive techniques to other operations. The first report of laparoscopic colon resection was by Jacobs et al. in 1991.[37] In 1993, within two years of the introduction of laparoscopic colon resection, the first sporadic cases of port-site metastasis (cancer recurrence at the laparoscopic incision sites) were reported.[38] Alexander et al. were the first to report on a 67-year-old man diagnosed with port-site metastasis after laparoscopic-assisted right colectomy for Dukes' C colon cancer.[39] This was followed by a report from O'Rourke et al., who described an 82-year-old woman with two port-site metastases, after resection for a Dukes' B adenocarcinoma.[40] Berends et al. reported a particularly alarming example of three tumor recurrences in only 14 patients.[41] These reports raised a great deal of concern, particularly in comparison with the low risk of wound recurrence in

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[37] Jacobs M, Verdeja JC, Goldstein, HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc (1991) 1:144-50.

[38] Zmora O. Wexner SD. Part I: Laparoscopic surgery for colon and rectal cancer. Current Problems in Cancer (2001) 25(5):286-309.

[39] Alexander RJ, Jaques BC, Mitchell KG. Laparoscopically assisted colectomy and wound recurrence [letter]. Lancet (1993) 341:249-50.

[40] O'Rourke N, Price PM, Kelly S, Sikora K. Tumor inoculation during laparoscopy [letter]. Lancet (1993) 342:368.

[41] Berends FJ, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy [letter]. Lancet (1994) 334:58.

open colectomy for cancer.[42] In the next two years, at least 35 cases of port-site recurrence were reported in the literature by Johnstone et al.,[43] raising the possibility that there was some unknown aspect of the laparoscopic approach that might actually compromise cure.

At the same time, a group of practiced colorectal surgeons with initial experience with the laparoscopic approach had been developing plans for a randomized controlled trial to evaluate cancer outcomes and potential benefits of the laparoscopic approach (Clinical Outcomes of Surgical Therapy (COST) Study Group). The issue of wound implants led the group of surgeons to review their own cases[44] to determine if the same wound issues had arisen in their practices. They analyzed their own results from 372 laparoscopic procedures performed for colorectal cancer from 1991 through 1995. With a mean follow-up of 22.6 months, Kaplan-Meier survival curves by tumor TNM stage were similar to those reported for open colectomy by the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)

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[42] Reilly WT, Nelson H, Schroeder G, Wieand HS, Bolton J, O'Connell MJ. Wound recurrence following conventional treatment of colorectal cancer: A rare but perhaps underestimated problem. Dis Colon & Rectum (1996) 39(2):200-07.

[43] Johnstone PA, Rohde DC, Swartz SE, Fetter JE, Wexner SD. Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. J Clin Oncol (1996) 14(6):1950-56.

[44] Fleshman JW, Nelson H, Peters WR, Kim HC, Larach S, Boorse RR, et al. Early results of laparoscopic surgery for colorectal cancer: retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) study group. Dis Colon & Rectum (1996) 39(suppl):53S-58S.

Program. There were four wound implants, for an overall incidence of 1.08%, or an incidence of 4 of 304 (1.3%) potentially curable patients. With this reassurance from their own experience that the laparoscopic approach did not entail higher incidences of wounds or tumor recurrences, the COST group proceeded with its randomized controlled trial.

Before the trial was concluded, however, there was a significant policy change. Both the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Endoscopic and Gastrointestinal Surgeons (SAGES) published policy statements in their respective journals, recommending that laparoscopic colectomy for curative intent should be performed only under the auspices of a randomized controlled trial or in the setting of careful prospective follow-up of outcomes.[45]

Results of the landmark U.S. randomized COST trial were published in the spring of 2004 and showed equivalent cancer outcomes in the open and laparoscopic groups of the study. The data suggested that the laparoscopic procedure was safe in experienced hands.[46] In the meantime, few laparoscopic colon resections for colon cancer had been performed in the general population, a result of the ASCRS and SAGES policy statements. A subsequent policy statement, after publication of the

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[45] American Society of Colon and Rectal Surgeons. Approved statement: laparoscopic colectomy. Dis Colon & Rectum (1994) 37:638.

[46] Nelson H, Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med (2004) 350:2050-59.

results of the randomized COST trial, noted that the trial had shown equivalent results "in experienced hands" and recommended that laparoscopic resection of colon cancer with curative intent should be performed only by surgeons with experience with at least 20 procedures for benign disease.[47]

This episode demonstrates the relevance of case reports and case series to medical researchers and professionals. In retrospect, it appears that, in an attempt to allow patients to benefit from minimally invasive techniques, some surgeons did not fully comply with accepted oncologic principles in colon cancer operations and may have taken short-cuts with the extent of resection. The initial case reports were instrumental in identifying the issue of tumor recurrence and in prompting both further investigation and also significant policy change by two national surgical societies.

The example of laparoscopic procedures for colon cancer has a direct parallel to the instant case. The review article by Johnstone et al., describing 35 cases of port-site recurrences after laparoscopic colectomy for colon cancer,[48] was instrumental in compiling multiple case reports and small case series and indicating the existence and growing nature of the

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[47] American Society of Colon and Rectal Surgeons. Approved statement: laparoscopic colectomy for curable cancer. Dis Colon & Rectum (2004) 47(8):A1; American Society of Colon and Rectal Surgeons. Approved statement: laparoscopic colectomy for curable cancer. Surg Endosc (2004) 18(8):A1.

[48] Johnstone PA, Rohde DC, Swartz SE, Fetter JE, Wexner SD. Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. J Clin Oncol (1996) 14(6):1950-56.

problem. Similarly, a case report by Jafek et al. was important in alerting medical professionals to the risks of Zicam.[49] In addition, Davidson et al. published a report and review article describing 25 patients who developed acute-onset permanent anosmia after intranasal application of zinc gluconate gel.[50] In addition to the 25 cases observed in their institution, they reviewed other cases noted in the literature, bringing the total number of reported cases to 88. Just as Johnstone et al. recognized port-site recurrences as an unusual phenomenon after surgery for colon cancer, medical researchers also recognized the rare nature of acquired permanent anosmia and collated evidence to suggest a common causative agent. Thus, the example of Zicam and anosmia illustrates the importance of case reports and case series to medical professionals in providing material information that can justify further action.

In sum, medical professionals and researchers do not limit the data they consider to the results of randomized clinical trials or to statistically significant evidence. Rather, they take into account all medically relevant data. Accordingly, statistical significance should not be used as a rigid standard for defining the materiality requirement for reasonable investors in the context of medical risks.

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[49] Jafek BW, Linschoten MR, Murrow BW. Anosmia after intranasal zinc gluconate use. Am J Rhinol (2004) 18(3):137-41.

[50] Davidson TM, Smith WM. The Bradford Hill Criteria and Zinc-Induced Anosmia: A Causality Analysis. Arch Otolaryngol Head Neck Surg (2010) 136(7):673-76.

CONCLUSION

The judgment below should be affirmed.

Respectfully submitted,

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November 2010