

**League of United Latin-American Citizens
(LULAC)**

**Community Bioethics Dialogue: Patient-Centered
Outcomes Research**

Final Report December 31, 2015

*A Partnership between the League of United Latin-American Citizens
(LULAC), Galveston, and the
Institute for the Medical Humanities, University of Texas Medical
Branch, Galveston*

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Introduction

To carry out the project, an Academic Support Team from University of Texas Medical Branch-Galveston (UTMB) formed a partnership with the League of United Latin American Citizens (LULAC). The ethical questions to be addressed were determined by the funding agency according to the initial grant proposal. The main ethical questions addressed were, in general:

- What ought to be the role of patient-centered outcomes research (PCOR) and comparative effectiveness research (CER) in guiding health policy in the U.S.?
- How should PCOR and CER function in connection with the physician-patient relationship?
- What role, if any, should commercial interests play in determining PCOR and CER policy?

Our Process

The Academic Support Team met with LULAC's executive leadership between May and August 2015 to plan the dialogues. LULAC's executive leadership oversaw the recruitment of participants from the organization and provided meeting facilities. Since the project was overseen by the Sealy Center on Aging at UTMB, it was agreed that all participants should be 65 years of age or older. An active LULAC member was the facilitator for the group, and the Academic Support Team provided facilitator training.

Prior to the start of the dialogues, the Academic Support Team compiled a list of articles from medical journals and the lay press related to ethical issues in PCOR and CER (Appendix 1). All were provided with one-page summaries of these readings, as well as the articles and case studies.

The dialogues occurred for two hours each week for six weeks during September and October 2015. Case studies formed the major basis for discussion during each session (Appendix 2). We were also encouraged to do independent research and to discuss our deliberations with friends and family in between sessions. The Academic Support Team provided a recorder, and other members of the Academic Support Team attended and took notes during sessions.

Before the final dialogue session, the Academic Support Team compiled a list of ethical values taken from notes during Sessions 1-5. The list was provided to us prior to Session 6 and we were asked to agree or disagree with each ethical value statement, and if we agreed, to rank the statement as having high, medium, or low priority. We discussed the list extensively during Session 6, and the results formed the basis for the first draft of this report. The draft was presented to us on November 4, 2015, and any further disagreements resolved at that time.

This final report is the result.

Major Ethical Conclusions

The statements in this section include ethical values which we were nearly unanimous (at least 14 of 15 voting members) to include, and to which all or most of us assigned the highest priority.

Physicians and Patients. The recurring theme from our meetings was the need for PCOR and CER to have a positive impact on the care of patients and the improvement of

patients' health. We believe that for those goals to be achieved, certain things must be true about how physicians and other health professionals relate to patients.

- Patient-centered care means that physicians have a responsibility to listen to their patients and provide truthful information about diagnoses, treatment options, and costs. Sufficient time needs to be allowed in the clinical setting for this dialogue to occur.
- Patients have a responsibility for becoming informed regarding their health and participating actively in decisions rather than blindly trusting physicians.
- Ideal decision-making requires a team approach that includes the individual's family and all health care providers.
- Physicians should inform patients of all of the treatment options, including the costs. Since quality of life means different things to people, everyone should be able to personalize their treatment choices.
- People should be able to talk to their physicians about all aspects of their care, including end-of-life choices.

Medications. Issues associated with medications and the pharmaceutical industry present particular issues for consideration. Overall, we believe that medications should be affordable and the system should support the release of safe and effective drugs for public use.

- Insurers should allow patients to take the medications that will probably work best without having to try cheaper drugs first.
- The FDA should not approve a new drug if it cannot be shown to improve patient-centered outcomes.

The Health Care System. Other important ethical considerations relate to the health care system as a whole, which includes policy makers; hospitals; Medicare/Medicaid, insurance and

other payers; physicians, nurses, and other professionals and support personnel.

- The health care system should do everything possible to preserve the free choice of available treatments by each patient, and people should not have to deplete their savings to receive health care.
- If there are two available treatment options, the most conservative/least expensive should be tried before the other. If this option does not work, Medicare or other insurers should cover the more expensive option.

More Problematic Ethical Conclusions

For some of the other ethical issues we grappled with, it was harder to reach consensus. This was especially the case with a variety of issues: health care availability; payment for brand-name medications; other medication issues; balancing free choice and cost containment; drug availability for single individuals; medical tourism; balancing scientific evidence with individual patient testimony; and physician-assisted suicide.

Health care availability. Most of us believe that we have an ethical problem in this country because the rich get better health care than the poor, although we range on the priority that should be given. Others believe that this is not an issue, believing that this cannot be proven due to the complexity of the system and the number of people involved.

Payment for brand-name medications. Overall, we agree that Medicare should pay for brand-name medications only when the patient is unable to use the generic equivalent. However, only two-thirds of us believe that this has the highest priority. When it comes to the physician's responsibility for identifying cheaper drugs that will work best, the same number agreed that this should have the highest priority.

Other Medication issues. While all of us believe that commercial influence over

physicians is a serious ethical problem, only two-thirds believe this has the highest priority.

Balancing free choice and cost containment. We recognize that the health care system is affected by costs. However, we disagreed on its priority, with some believing that a less expensive treatment should always be tried before the more expensive one. We believe that individuals with a terminal illness should have the option to choose expensive treatments even if they are unlikely to provide benefit.

Drug availability for single individuals. About two-thirds of us believe that a drug should be available if it helps just one person, with the rationale that “I might be that person.” Others believe that this is not reasonable, given the complexity of the system.

Medical tourism. Some of us have read about medical tourism, and we believe that this may be an option, with some of us concluding that Medicare should consider paying for international treatments if the costs are lower and results are comparable. Others believe that this is not a priority.

Balancing scientific evidence with individual patient testimony. On the one hand, we believe that patient testimonies should be considered; on the other hand, we believe that scientific evidence provides significant and reliable evidence of a treatment’s effectiveness. Most of us believe that personal testimonies should be considered equally with scientific evidence. At the same time, we should consider the source of the testimony; as an example, when a drug company pays someone to travel to provide evidence at a hearing; we would be suspicious of the motives. Treatment options should be decided between the physician and the patient, even if scientific studies conclude that likely benefits are limited.

Physician-assisted suicide. While we were participating in the dialogues, California’s governor signed legislation to allow physician-assisted suicide. This resulted in an active

discussion, with some concluding that physicians should not be allowed to play God. At the same time, we do not believe that patients should be allowed to suffer in their final stages of life; rather, physicians have a responsibility to make people comfortable.

Comments on the Community Bioethics Dialogues

This has been a good experience, and here are our individual testimonies:

- It enhanced a lot of the information that I already had gathered, and then it clarified other information and misconceptions.
- I learned a lot more about the way things on both sides – on our side how things are run, on our side, and on the medical side how things are manipulated by drugs – it can be overwhelming – you have to pay so much to companies who are going to try to help a human being out – how can money be of value on that – it depends – how can people try to make a lot of money. I had never heard about it – it opened the door for me to understand.
- I enjoyed it – the only thing that I am wondering – does anything change? There are still manufacturers that are making billions, and there is no improvement. I'm hoping they make changes because they are draining the Medicare system.
- I said at the very beginning that I have always trusted my doctor, and I have learned that I need to take responsibility for my own health and look at different options and not just be so trusting.
- I learned that I need to pay more attention to the doctor instead of just my children – I need to be more alert and take notes.
- I knew most of the stuff, but I have become a little bit more aware of other things. All in all, I have learned quite a bit – it has opened my eyes, mainly don't leave it up to the

doctor. You know your own body – you know what’s going on in your body. If they say something, I know what is going on. If a medication is not doing what it is supposed to, you need to let him know and not just take it for granted, because they are only human and do not know unless you say something. You’ve got to take charge – only you know what is going on.

- Coming from a total distrust of physicians because of past experiences, I think I have regained a little bit of confidence just listening to other people’s stories and knowing that everything has a reason behind it – the reasons doctors do things and drug companies – so I hope it’s restored my faith in the medical profession.
- It was a good experience – a lot of things have happened in my own life, and I do have a wonderful doctor. She really cares about her patients, and you can talk to her. If other doctors could be like her, it would be great.
- You have your way of thinking – it’s not just your way – but you make your decisions according to how you feel. I’ve always believed in trusting the doctors, but they’re not always perfect.
- To me – it was interesting – I learned a lot about cancer – it does not run in my family. Every day I came, it was more interesting. I changed my mind a little bit – some of those pills are really expensive. If I didn’t have insurance like I have, I would have to do without. I enjoyed it and learned a lot.
- I’m really blessed because I don’t have any illness – I’ve never been in a situation like some of you all with family and friends – so I don’t have a personal basis. I have done a lot of this on my own. I’m not the demanding type, but I share what I have. What I have learned – I have always been in favor of generic drugs because of the cost, and

being on a fixed income. I knew about decision-making, but what I have learned is that if I ever have a terminal illness, I should get a second opinion.

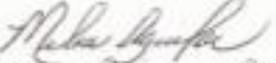
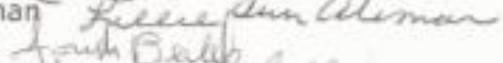
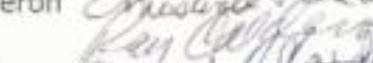
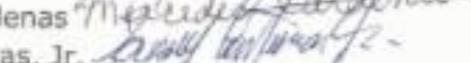
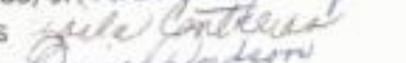
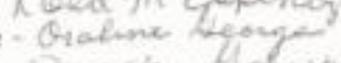
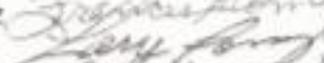
- I think we learned a lot, and still we have a lot more to learn – we have only scratched the surface. I learned that the pharmaceutical companies control their own destiny, the prices, they have the influence, the lobbyists. The people that are making the laws and what we should know – they have better insurance – they have better care than we get. What they are offering us, they're not going to get. I've always believed that if you're dying, don't let someone suffer – make them comfortable. I think we all learned a lot, and there's more we can learn – someone might read this. I hope we can get into it a lot more, and that's how we can change things.

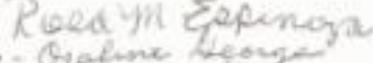
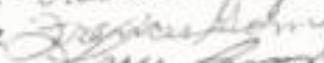
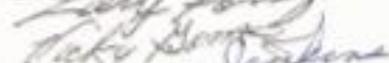
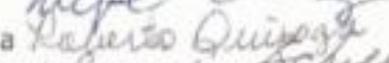
We have all learned a great deal from the readings and from discussing health care issues with each other. We are more aware of news stories, and are paying attention. Many of us have extended the discussions with our families about health care options and choices. We believe that this process should continue, and be made available to others.

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Appendix 1.

List of Background Readings and Session

Topics

Topic List: Community Bioethics Dialogue on PCOR/CER

Week 1

Case Studies: ALLHAT, Generic Drugs

Topic: Ethics and cost containment: Is there an ethical mandate to contain health care costs?

Brody, H. "Is There an Ethical Mandate to Contain Health Costs in the U.S.?"

Topic: What is PCOR/CER?

Coelho, Tony. "A Patient Advocate's Perspective on Patient-Centered Comparative Effectiveness Research." *Health Affairs* 29:1885-1890, 2010.

Wu, Albert W, Claire Snyder, Carolyn M Clancy, and Donald M Steinwachs. "Adding the Patient Perspective to Comparative Effectiveness Research." *Health Affairs (Project Hope)* 29, no. 10 (October 2010): 1863–1871. doi:10.1377/hlthaff.2010.0660.

Supplementary:

Washington, A. Eugene, and Steven H. Lipstein. "The Patient-Centered Outcomes Research Institute — Promoting Better Information, Decisions, and Health." *New England Journal of Medicine* 365, no. 15 (2011): e31. doi:10.1056/NEJMp1109407.

Week 2

Case Study: Meniscus Tear

Topic: The potential impact of CER/PCOR on patient autonomy and the doctor-patient relationship (How can doctors continue to be patient-centered while applying population-based research? How can we make the research and its application more patient-centered? How would participants prefer to see PCOR results implemented in individual care/ doctor-patient decision-making? Should doctors and patients be tied down to what evidence shows works best?)

- Bensing, J. "Bridging the Gap. The Separate Worlds of Evidence-based Medicine and Patient-centered Medicine." *Patient Education and Counseling* 39, no. 1 (January 2000): 17–25.
- Chen, Pauline W. "A Tool to Strengthen the Doctor-patient Relationship." *The Hastings Center Report* 39, no. 6 (November 1, 2009): 15–17.
- Katz, Jeffrey N., et al. "Surgery Versus Physical Therapy for a Meniscal Tear and Osteoarthritis. New England Journal of Medicine 368, no. 18 (August 15 2013): 1675-84.
- Parker, Lisa S., and Howard Brody, "Comparative Effectiveness Research: A Threat to Patient Autonomy?" *Health Progress* 92 (5): 64-71, 2011.
- Sihvonen, Raine, et al. "Arthroscopic Partial Meniscectomy Versus Sham Surgery for a Degenerative Meniscal Tear." *New England Journal of Medicine* 369, no. 26 (2013): 2515-24.
- Spindler, Kurt P., et al. "Prognosis and Predictors of ACL Reconstructions Using the Moon Cohort: A Model for Comparative Effectiveness Studies." *Journal of Orthopaedic Research* 31, no. 1 (2013): 2-9.
- "Left Knee Medial Meniscectomy." In *Medical Evaluators of Texas: Independent Review*, September 17 2014.

Supplementary:

- Buetow, Stephen, Linn Getz, and Peter Adams. "Individualized Population Care: Linking Personal Care to Population Care in General Practice." *Journal of Evaluation in Clinical Practice* 14, no. 5 (October 2008): 761–766. doi:10.1111/j.1365-2753.2007.00938.x.
- Payne, Richard. "The Quality Mantra: Proceed Carefully." *The Hastings Center Report* 39, no. 6 (November 1, 2009): 7-20.
- Weeks, William Brinson, and William A Nelson. "Ethical Issues Arising from Variation in Health Services Utilization at the End of Life." *Frontiers of Health Services Management* 27, no. 3 (2011): 17–26.

Week 3

Case Study: Rapid Approval of a Cancer Drug (Iressa)

Topic: Pros: Using CER as a rationing criterion to reduce costs (some of these articles are not necessarily "pro" but focus on how cost management might be implemented using CER). Many of these articles also address the reasons why cost might be problematic.

Brody, H. “Two Approaches to Rationing by Appeal to Evidence of Effectiveness”

Garber, Alan M, and Harold C Sox. “The Role of Costs in Comparative Effectiveness Research.” *Health Affairs (Project Hope)* 29, no. 10 (October 2010): 1805–1811.

Supplementary:

Buyx, Alena, Daniel Friedrich, and Bettina Schöne-Seifert. “Rationing by Clinical Effectiveness.” *BMJ* 342:531-533, 2011.

Kreis, Julia, and Harald Schmidt. “Lessons from Abroad.” *The Hastings Center Report* 39, no. 6 (Nov-Dec 2009): 20–22.

Robinson, James C. “Comparative Effectiveness Research: From Clinical Information To Economic Incentives.” *Health Affairs* 29, no. 10 (October 1, 2010): 1788–1795.

Topic: Cons: Using CER as a rationing criterion to reduce costs

Mikochik, Stephen L. “Rationing Human Life: Health Care Reform and People with Disabilities.” *Issues in Law & Medicine* 26, no. 3 (2011): 199–205.

Topic: Cons: The involvement of private industry in the PCORI (conflict of interest)

Selker, Harry P., and Alastair J.J. Wood. “Industry Influence on Comparative-Effectiveness Research Funded Through Health Care Reform.” *New England Journal of Medicine* 361, no. 27 (2009): 2595–2597.
doi:10.1056/NEJMp0910747.

Week 4

Case Study: Proton Beam Radiation

Topic: Inherent limitations of PCOR/CER methodology (averages, unable to predict individual patient outcomes; limits of RCT method; defining “effective”; etc.)

Alexander, C. Caleb, and Randall S. Stafford. “Does Comparative Effectiveness Have a Comparative Edge?” *JAMA* 301:2488-2490, 2009.

Berlinger, Nancy, and Anne Lederman Flamm. “Define ‘Effective’: The Curious Case of Chronic Cancer.” *The Hastings Center Report* 39, no. 6 (Nov-Dec 2009): 7-20.

Susan Gilbert. “The Nesting-Egg Problem: Why Comparative Effectiveness Research is Trickier than It Looks.” *Hastings Center Report* 39, no. 6 (Nov-Dec 2009):11-14, 2009.

Supplementary:

Saver, Richard S. “Health Care Reform’s Wild Card: The Uncertain Effectiveness of Comparative Effectiveness Research.” *University of Pennsylvania Law Review* 159:2147-2207, 2011.

Saver, Richard S. “The New Era of Comparative Effectiveness: Will Public Health End up Left Behind?” *The Journal of Law, Medicine & Ethics: a Journal of the American Society of Law, Medicine & Ethics* 39, no. 3 (2011): 437–449.
doi:10.1111/j.1748-720X.2011.00613.x.

Week 5

Case Study: Advanced Cancer treatment (Erbitux)

Topic: Conclusions: Ethical values that should guide policy decisions about the use of PCOR/CER (these are articles that cover general ethical patient care)

Potera, Carol. “Dignity-driven Decision Making Improves Advanced-illness Care.” *The American Journal of Nursing* 112, no. 9 (September 2012): 16.
doi:10.1097/01.NAJ.0000418910.72042.cf.

Vladeck, Bruce C, and Erin Westphal. “Dignity-driven Decision Making: a Compelling Strategy for Improving Care for People with Advanced Illness.” *Health Affairs (Project Hope)* 31, no. 6 (June 2012): 1269–1276.
doi:10.1377/hlthaff.2012.0173.

Supplementary:

“CER Ethics Controversy Spills over to Health Debate.” *Clinical Trials Administrator*, October 1, 2009. Academic OneFile.
[http://go.galegroup.com/ps/i.do?id=GALE%7CA214561483
&v=2.1&u=txshracd2598&it=r&p=AONE&sw=w](http://go.galegroup.com/ps/i.do?id=GALE%7CA214561483&v=2.1&u=txshracd2598&it=r&p=AONE&sw=w).

Patrick S. Duggan, Gail Geller, Lisa A. Cooper, and Mary Catherine Beach. “The Moral Nature of Patient-Centeredness: Is It ‘Just the Right Thing to Do?’” *Patient Education and Counseling* 62:271-276, 2006.

Wynia MK, Von Kohorn I, Mitchell, P. “Challenges at the Intersection of Team-based and Patient-centered Health Care: Insights from an IOM Working Group.” *JAMA* 308, no. 13 (October 3, 2012): 1327–1328.
doi:10.1001/jama.2012.12601.

Week 6

Topic: Review and Decision on Final List of Ethical Values and Priorities

Appendix 2.

Case Studies

Study Example

Physicians continue to prescribe expensive brand-name drugs for high blood pressure despite solid evidence that older, cheap generics actually work better, experts said.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was carried out between 1994 and 2002, and was funded by the National Heart, Lung and Blood Institute of the National Institutes of Health.

Experts claimed that ALLHAT is a good example of “patient-centered outcomes research” because it did not look only at whether a drug lowered blood pressure. The trial studied outcomes that matter most to patients—death, heart attack, stroke, and the development of other serious diseases of the heart and blood vessels. ALLHAT also qualified as comparative effectiveness research (CER) because it asked which of several alternative treatments did better in preventing these bad outcomes.

ALLHAT was a real advance, experts commented, because the first research studies of treating high blood pressure (hypertension) were carried out with older classes of drugs, diuretics and beta-blockers. These trials showed benefits of drug treatment in preventing later heart attack and strokes. Since then, newer classes of drugs were introduced also to treat hypertension. The classes of special interest in ALLHAT were angiotensin-converting-enzyme (ACE) inhibitors and calcium channel blockers. No one had studied whether these newer drugs were better than the older classes of drugs in preventing the bad outcomes associated with untreated hypertension.

The hypertension portion of the ALLHAT trial reported in 2002 involved 33,357 participants aged 55 or older who had hypertension and at least one other risk factor for developing heart disease. The participants were randomly assigned to receive one of three drugs: a generic diuretic (chlorthalidone); an ACE inhibitor (lisinopril); or a calcium channel blocker (amlodipine). They were then followed for 4 to 8 years.

The main outcome the study looked at was either death due to heart or blood vessel disease, or a heart attack. They found that this outcome occurred with equal frequency in people receiving any of the three drugs.

The study then looked at a number of other outcomes, such as stroke, heart disease without heart attack, and heart failure. They found that for these other (secondary) outcomes, the diuretic (chlorthalidone) was superior to either of the other two drugs for at least some of the outcomes.

The authors concluded that overall, the diuretic (chlorthalidone) was superior to the other two drugs, and they also noted that it was considerably cheaper. They concluded that diuretics should be preferred as first-line treatment for hypertension.

After the ALLHAT trial was published, a number of papers appeared in medical journals disputing some of its findings and arguing that some of its methods were flawed. Experts consulted for this article, however, noted that the majority of these critical articles were written by physicians who had a financial tie to companies making the more expensive anti-hypertensive drugs. The majority of authorities who were financially neutral appeared to endorse the ALLHAT findings.

Reference

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting-enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981-2997, 2002

Case Study: Generic Drugs

The investigative reporting service ProPublica released (Nov. 18, 2013; <http://www.propublica.org/article/medicare-wastes-billions-on-name-brand-drugs>) their findings that just 913 physicians across the US are costing Medicare an extra \$300 million a year. How? By prescribing brand-name drugs instead of generics at a much higher rate. These same physicians also seem much more likely to have gotten payments from drug manufacturers, like fees for giving lectures favoring brand-name drugs.

Other data showed that the low-income portion of Medicare Part D, the prescription drug benefit, could save \$1.3 billion each year in just seven drug categories, if generic drugs were more widely used.

What does this have to do with comparative effectiveness research (CER)?

It's usually said that CER is a relatively new idea and needs to be expanded. But one form of what could be called CER has been going on routinely for many years without fanfare.

Whenever a brand-name drug goes off patent, meaning that generic drug companies can offer low-priced competition, the Food and Drug Administration requires scientific evidence of what's called bioequivalence before permitting the generic drugs into the market. "Bioequivalence" means that the science has to show that the generic drug, when ingested into the average human body, acts essentially the same way the brand-name drug does.

You could call this a form of CER because if the science is accurate, it means that the generic drug will show *comparative effectiveness* to the brand-name product—it should be just as good at treating whatever disease the patient has.

This form of CER is not properly considered patient-centered outcomes research because it only looks at the chemistry of how the drug is handled in the human body. Generic drug makers are not looking at the outcomes for the patients. But the ProPublica article mentioned two major clinic chains, in Chicago and Las Vegas, that stress cutting costs by using generic drugs wherever possible. Those clinics have reported success rates in lowering cholesterol and controlling diabetes that meet or exceed national standards—suggesting that the effects on patients and their health is, overall, equally good with generics.

Question: Given these facts, what do you think ought to be the policy for Medicare Part D?

1. Brand-name drugs cost more, so they must be better. Medicare should not use any generic drugs at all if a brand-name drug is available. The elderly, and especially low-income elderly who need a subsidy to afford drugs, deserve the very best.
2. Medicare should recommend prescribing generic drugs whenever available. However, if a patient wished to have a brand-name drug instead, the simple request should be enough to get the doctor to prescribe it and for Medicare to pay—there should be no requirement first to try the generic and see whether or not it works as well.
3. Medicare should favor prescribing generic drugs whenever available. Some patients, for reasons we don't fully understand, don't respond well to generics. For those patients who have been tried on generics and have not responded well, physicians should be allowed to prescribe brand-name drugs.

4. Medicare should pay only for generic drugs whenever available. Any patient who wants a brand-name drug instead of a generic, for whatever reason, should pay for it out of pocket.

Case Study: Meniscus Tear

Jane is a committed exercise buff, and runs regularly. One day, in the middle of her run, she feels a “pop” in her knee. She does not think too much about it, but slows to a walk and heads home. As the day progresses, her knee continues to hurt and swell significantly. She also has trouble straightening her leg fully.

The next day, a friend convinces Jane to go to the doctor, and tells her she should ask for an Magnetic Resonance Imaging (MRI), which will provide a detailed look at the extent of the injury. Jane is part of a Health Maintenance Organization (HMO) that requires her to see the Primary Care Physician (PCP) first. She is able to get an appointment, and the doctor checks out her knee. Based on the symptoms, the doctor concludes that she has probably torn the meniscus, a piece of cartilage that stabilizes and cushions the joint. When Jane asks if an MRI will be done, the physician responds that it is not necessary – the cost is high, and the diagnosis is fairly certain based on Jane’s limited motion. Since this is an HMO, Jane will not receive the MRI unless she is willing to pay the cost of the test herself – about \$3,000. She decides to delay the test at this point.

The physician tells Jane that a meniscus tear in the knee can be treated in one of two ways:

- Physical therapy: the patient is provided with an exercise regimen to strengthen the affected area; or
- Surgery: the meniscus is repaired surgically, either with arthroscopic means or open incision.

The physician recommends that Jane initiate physical therapy, and provides a referral to the group’s therapist. When Jane returns home, she investigates the injury by checking various websites. She learns that this is a common injury, and affects people particularly as they age. Over 40% of people over 65 have experienced this injury. She also notes that the physician has given her good advice regarding treatment options. She decides to follow the doctor’s recommendation, and visits the physical therapist, who recommends a regimen of daily exercises. Happily, Jane’s knee gets stronger, and within a few months, her knee is back to normal.

In this week’s readings, there is a different approach. In the Medical Evaluators review, we see that the physician has determined that the patient is considered inappropriate for the conservative therapy (exercise) without an actual trial to determine whether exercise helps the patient. However, the insurer has denied the request for surgical benefits, requesting that exercise therapy be tried.

In the Sivhonen et al article, a study of those with meniscus tears but no osteoarthritis showed that those having “sham” surgery had essentially the same outcome as those with actual surgery. A different study (Katz et al) of those with accompanying osteoarthritis showed that physical therapy was still successful in most cases.

In Patient Centered Outcomes and Comparative Effectiveness Research, the intent is to have objective evidence for preferred treatments. At this time, these studies support the recommendation for conservative therapy (exercise regimen) followed by surgical intervention only if it is necessary.

Question: Considering these readings:

1. What role does a person have in requesting tests or specifying treatment options? Should a patient be able to demand a more expensive test even though the outcome is fairly certain? Should a patient that is not interested in exercising be able to request a surgical repair?
2. A randomized, controlled study is the only really reliable way to find out about the comparative effectiveness of these two treatments. We should continue with the standard of care of recommending physical therapy, followed by surgical intervention only if physical therapy does not work. If in the future, a randomized, controlled trial shows no difference, we can then re-evaluate this policy.
3. The observational studies indicate that surgery offers limited benefits in most cases despite being more expensive. Since there is as yet no proof at all that surgery is always a better therapy, we should require all patients to try physical therapy, and *not* routinely pay for it with Medicare or insurance dollars. If after more research is done, there turn out to be clear advantages to surgical intervention, we can then re-evaluate this policy.

Katz, Jeffrey N., Robert H. Brophy, Christine E. Chaisson, Leigh de Chaves, Brian J. Cole, Diane L. Dahm, Laurel A. Donnell-Fink, Ali Guermazi, Amanda K. Haas, Morgan H. Jones, Bruce A. Levy, Lisa A. Mandl, Scott D. Martin, Robert G. Marx, Anthony Miniaci, Matthew J. Matava, Joseph Palmisano, Emily K. Reinke, Brian E. Richardson, Benjamin N. Rome, Clare E. Safran-Norton, Debra J. Skonieczki, Daniel H. Solomon, Matthew V. Smith, Kurt P. Spindler, Michael J. Stuart, John Wright, Rick W. Wright, and Elena Losina. "Surgery Versus Physical Therapy for a Meniscal Tear and Osteoarthritis.[Erratum Appears in N Engl J Med. 2013 Aug 15;369(7):683]." *New England Journal of Medicine* 368, no. 18 (August 15, 2013): 1675-84.

Sihvonen, Raine, Mika Paavola, Antti Malmivaara, Ari Itala, Antti Joukainen, Heikki Nurmi, Juha Kalske, Teppo L. N. Jarvinen, and Group Finnish Degenerative Meniscal Lesion Study. "Arthroscopic Partial Meniscectomy Versus Sham Surgery for a Degenerative Meniscal Tear." *New England Journal of Medicine* 369, no. 26 (December 26, 2013): 2515-24.

Case Study: Rapid Approval of a Cancer Drug

Iressa (generic name: gefitinib) is one of a new class of drugs for cancer treatment. Its manufacturer, AstraZeneca, asked for approval from the U.S. Food and Drug Administration (FDA) to sell the drug for treatment of non-small-cell lung cancer, the most difficult to treat form of lung cancer. The drug was intended as a third-line drug to be used in the most advanced cases of the disease, after two previous types of chemotherapy have failed.

FDA rules allow a company to seek approval under a fast-track program if the drug is a novel drug and addresses a serious, unmet medical need. For normal FDA approval, a cancer drug might have to be tested on many hundreds of patients and shown to improve survival. For the fast-track review, it might only be necessary to show in a smaller number of patients that the drug slows tumor growth. If a drug is approved on this fast-track basis, a company may be required to run further studies after the drug is on the market to prove that it's really effective. If the drug does not do well in those follow-up studies, the FDA could then withdraw the market approval.

AstraZeneca originally sought fast-track approval in 2002 and sent the FDA the results of a study, that showed that in 139 advanced lung cancer patients, Iressa slowed tumor growth in only about 10 percent. Experts who had recommended this standard for fast-track approval had stated earlier that in order to win approval, ordinarily a drug had to show tumor slowing in 20-30 percent of patients.

Apparently AstraZeneca was rather sure it would get quick approval of Iressa and so began a larger-scale study, called INTACT, which enrolled 2000 subjects and looked at survival as well as tumor shrinkage. The INTACT study had been completed as of September, 2002 and so the FDA had access to that information as it studied approval of Iressa. The INTACT study showed, unlike the earlier smaller study, that Iressa had no effect on tumor shrinkage. Worse, the drug also was shown not to improve survival.

The FDA scientific advisory committee considered the evidence about Iressa at a hearing on September 24, 2002. At that meeting, a number of cancer patients testified. Two patient organizations had identified these patients and paid their expenses to come to Washington to attend the hearing; both those organizations had received grants from AstraZeneca. Six patients testified how good a drug Iressa was in their experience and how they credited it with saving their lives. The scientific committee voted 11-3 to approve Iressa for marketing.

By December, 2004, there had been several new developments. First, Iressa had been found to cause a fatal pneumonia in about 2 percent of patients. Second, a further study had been done of Iressa's effectiveness which also showed it did not prolong survival. Third, there was now a new drug for non-small-cell lung cancer manufactured by another company, so Iressa was no longer the only chance for patients with that disease. The FDA advisory committee reviewed all this information, and could at that time have recommended that Iressa be taken off the market, but instead recommended that the drug be allowed to stay on the market.

When Iressa was in wider use, it reportedly cost about \$1800-2000 per month, and had to be taken indefinitely.

Questions

1. Tumor size is not what is usually viewed as a "patient-centered outcome." Most people with cancer would be happy to learn that their tumors were shrinking, but only because

they thought that this had to mean that they'd either live longer, or else have fewer bad symptoms. If tumors shrink temporarily but the patient does not live any longer nor have any improvement in quality of life, most would be disappointed. Should the FDA be allowed to approve a drug based on this sort of non-patient-centered outcome?

2. The FDA committee's vote was heavily swayed by the testimony of actual patients taking Iressa. This testimony, apparently, was allowed to overcome scientific evidence showing no benefit from the drug. Isn't this the way it should be—if we believe in patient-centered outcomes, then we have to listen to patient's personal testimony and give that at least equal weight with large-scale scientific studies?
3. Some would say that the funding by the drug company was a biasing or distorting influence in the scientific hearing. Is this correct? Some would say that patients deserve to be heard and that all the drug company was doing was making it financially possible for these patients to travel to attend the hearing.
4. *Comparative* effectiveness research assumes that we have two drugs which each individually seems to be effective, and we want to know if one is more effective (or safer) than the other. Presumably Iressa could not undergo comparative effectiveness research because studies showed it not to be effective, period (at least in terms of survival). What role, if any, should comparative effectiveness research play in drugs for serious diseases like cancer?

Adapted from: Courtney Davis and John Abraham, "Desperately Seeking Cancer Drugs: Explaining the Emergence and Outcomes of Accelerated Pharmaceutical Regulation." *Sociology of Health and Illness* 33:731-747, 2011.

Case Study: Proton Beam vs. Standard Radiation Treatment for Prostate Cancer

Background: One treatment for prostate cancer that hasn't spread outside the prostate gland is radiation. This can be given in a standard way (intensity-modulated radiation therapy). Recently, with great fanfare, many hospitals have invested in proton-beam machines, that deliver radiation from a particle accelerator that costs about \$100-180 million to build. As a result, hospitals have to charge about twice as much for proton-beam therapy to recover their capital costs.

No controlled trials currently show that proton-beam radiation produces results that are any better than standard radiation. One type of trial that could address this question is a randomized clinical trial, where patients with prostate cancer are randomly assigned to standard or to proton-beam treatment. A different type of study could be done much more cheaply and quickly, by looking for existing patient outcomes in a large Medicare database called SEER. Advantages of a controlled randomized trial include being able to measure exactly what you want to, and being able to be sure that the difference in treatment caused any difference in outcomes, instead of those differences being due to some other variable that you don't know. Advantages of an observational study with an existing database, besides convenience, include very large numbers of patients and knowing that the treatments and outcomes are representative of what happens in the "real world" instead of the tightly controlled, artificial environment of a medical research study.

A large randomized controlled trial comparing proton-beam and standard radiation for prostate cancer is now underway but results are not expected for several years.

The study: A group published a comparative-effectiveness observational study comparing standard radiation with proton-beam therapy in 2012, based on an observational review of SEER data reflecting patient experience during 2000-2008. They were able to compare information about 6666 men treated with standard radiation and 684 men who received the proton-beam treatment. They found information about what happened to these men for about 45 months after their radiation treatment.

The outcomes the study looked at were common side effects of radiation treatment (bowel problems, hip fracture, urinary incontinence, and erectile dysfunction). They used whether the patient started a new course of prostate cancer treatment more than 9 months after completing radiation as a signal for possible recurrence of the cancer. (Since most men with localized prostate cancer survive more than 5 years after initial treatment, they were not able to use life or death as a study measure.)

The study results showed no difference between standard radiation therapy and proton-beam therapy in hip fracture, incontinence, erectile dysfunction, or need for further cancer treatment; the proton-beam group did have more bowel problems.

Question: Taking the results of this study, which course of action would you favor?

1. A randomized, controlled study is the only really reliable way to find out about the comparative effectiveness of these two treatments. We should go on using both treatments and continue paying for the proton-beam therapy for patients who want it and have it recommended by their physicians. If in the future, a randomized, controlled trial shows no difference, we can then re-evaluate this policy.

2. The observational study reported above raises questions about whether proton-beam therapy offers any advantages over standard therapy despite being twice as expensive. Since there is as yet no proof at all that proton-beam therapy works better, we should regard proton-beam treatment as experimental only at this time, and *not* routinely pay for it with Medicare or insurance dollars. If after more research is done, there turn out to be clear advantages to proton-beam treatment, we can then re-evaluate this policy.

Sheets NC, Goldin GH, Meyer AM, et al. "Intensity-Modulated Radiation Therapy, Proton Therapy, and Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer." *JAMA* 307:1611-1620, 2012.

Case Study: Advanced Cancer

Oncologist Dr. Tito Fojo and bioethicist Christine Grady wrote:

The all too common practice of administering a new, marginally beneficial drug to a patient with advanced cancer should be strongly discouraged. In cases where there are no further treatment options, emphasis should be first on quality of life and then cost. Although we recognize that oncologists are faced every day with dying patients who still want to pursue further therapy, we must avoid the temptation to tell a patient that a new drug *E* is available if there is little evidence that it will work better than established drugs... that could be offered at a miniscule fraction of the cost and with possibly less toxicity.

To illustrate “marginally beneficial,” they report a large trial of the drug cetuximab (Erbix) for non-small-cell lung cancer. When added to two other standard drugs, cetuximab extended overall survival by an average of 1.2 months. Patients receiving cetuximab had more fevers, rashes, diarrhea, and reactions to the drug infusions. The cost of a full course of treatment with cetuximab at the time was about \$80,000.

Fojo and Grady went on to distinguish several things we could mean when we say that a cancer treatment is “effective”:

- The treatment could extend overall survival. As the cetuximab example shows, many drugs are approved that show only very small improvements in overall survival, so we could argue about how much survival on average is needed for a drug to be considered more “effective” than other drugs.
- A treatment could extend progression-free survival, the length of time a patient lives before the cancer starts to grow again. Most people would presume that if a drug extends progression-free survival, it must also extend overall survival, but a number of drugs have been disappointing in this regard.
- A treatment could allow a patient to live with an acceptable quality of life. As with cetuximab, some drugs that extend survival only slightly do so at a serious cost in terms of side effects and reducing quality of life for many patients.

Questions:

1. In the current system, for those patients who have insurance and can get access to an oncologist for cancer treatment, the patient and oncologist together decide on what counts as a true benefit, what treatments should or should not be used, and so on. Often this amounts to the oncologist deciding, as many patients simply defer to the oncologist. Is there any reason to change this present practice?
2. An increasing number of cancer patients search on-line to find information about the drugs their oncologist recommends. What would count as an adequate on-line review of a drug like cetuximab, so that patients could make ideally informed choices?
3. Do you agree with Fojo and Grady that the cost of drugs ought to be considered as part of the judgment about whether they should be used?

4. Fojo and Grady's recommendation, that oncologists might simply not mention to patients with advanced cancer that some newer, expensive drugs exist if there's no good evidence that they extend survival more than existing drugs, might be viewed as inappropriately robbing patients of "hope" or their "last chance." How do you assess these objections?

Fojo T, Grady C. How Much Is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the \$440 Billion Question. *J Natl Cancer Inst* (2009) 101 (15): 1044-1048.