THE MYTH OF AVERAGE:

Why Individual Patient Differences Matter

National
Pharmaceutical
Council

Acknowledgments

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About the National Pharmaceutical Council

The National Pharmaceutical Council is a health policy research organization dedicated to the advancement of good evidence and science, and to fostering an environment in the United States that supports medical innovation. Founded in 1953 and supported by the nation's major research-based pharmaceutical companies, NPC focuses on research development, information dissemination, and education on the critical issues of evidence, innovation and the value of medicines for patients. For more information, visit **www.npcnow.org** and follow NPC on Twitter **@npcnow**.

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Introduction

When describing health care data or treatment side effects, one of the most common phrases we hear is “on average,” or “the average patient.” But as we learn more about treatments and optimal care, it’s very clear that most patients are not “average” at all.

Our bodies respond in different ways to the same treatment. One person might have bothersome side effects, while someone else will not; and another person’s condition might be successfully treated with one medicine, while the next person experiences no benefit from the very same treatment.

Treatment differences among patients are common, but not always considered when treatment decisions are being made. It’s important to know that even if treatment “A” works better for most people, treatment “B” might be better for others.

This “myth of average” has emerged as an important issue and has prompted research, analysis and discussion by the National Pharmaceutical Council, along with leading health organizations like the National Health Council, WellPoint, and others.

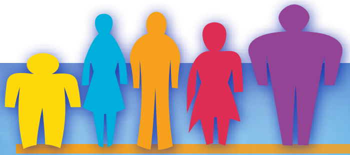
In this booklet, NPC has used these discussions to address questions such as:

- If you’re not “average,” how could that impact your treatment choices?
- What explains why individuals have different responses to the same treatments?
- How can comparative effectiveness research consider patient differences?
- What challenges do insurance companies face when providing coverage for patients with different responses?

Having patients and their caregivers involved in this discussion will help lead to a truly patient-centered health care system, which is why we have made this booklet available to you.

We encourage you to explore additional resources on our website, **www.npcnow.org**, and connect with us on Twitter **@npcnow**.

Dan Leonard
President
National Pharmaceutical Council

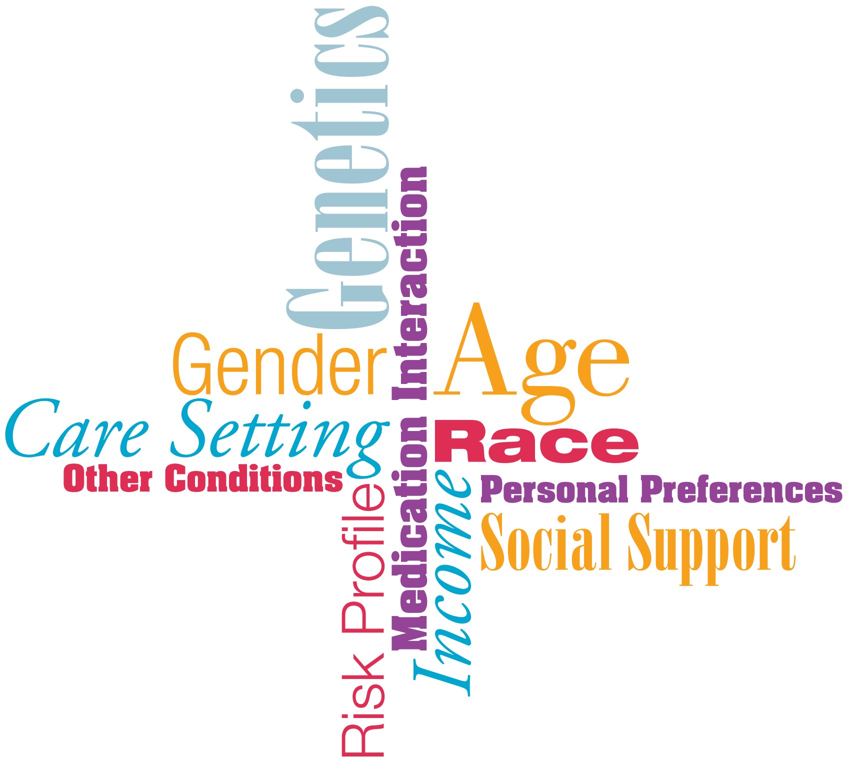


Heterogeneity and Individual Treatment Effects

What This Means

It's hard to be excited about being "average." But when you are facing a health challenge, being average can make your treatment decisions and management easier and more predictable. Being average means that your illness progresses like it does in most people, so you respond to treatments like most people, and your journey in achieving better health resembles what other patients are experiencing.

In the real world though, it's hard to find people who are "just like you." Each person is unique thanks to a multitude of factors, such as racial and ethnic backgrounds, age, genetics, chronic conditions, gender, environment, and even personal preferences when it comes to health treatments. These factors affect how we may respond to a certain treatment, although it may be difficult to explain why this occurs.



What does "heterogeneous" mean?

If you look in the dictionary:
het·er·o·ge·ne·ous *[het-er-uh-jee-nee-uhs, -jeen-yuhs*] adjective

1. Different in kind; unlike; incongruous.[1]

If you ask researchers:

1. Used in a general sense to describe the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies, or the variation in internal validity of those studies.
2. Used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance.[2]

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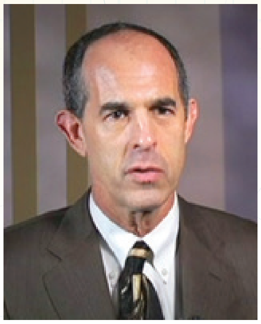
[1] Dictionary.com, http://dictionary.reference.com/browse/heterogeneous. Accessed February 13, 2013.

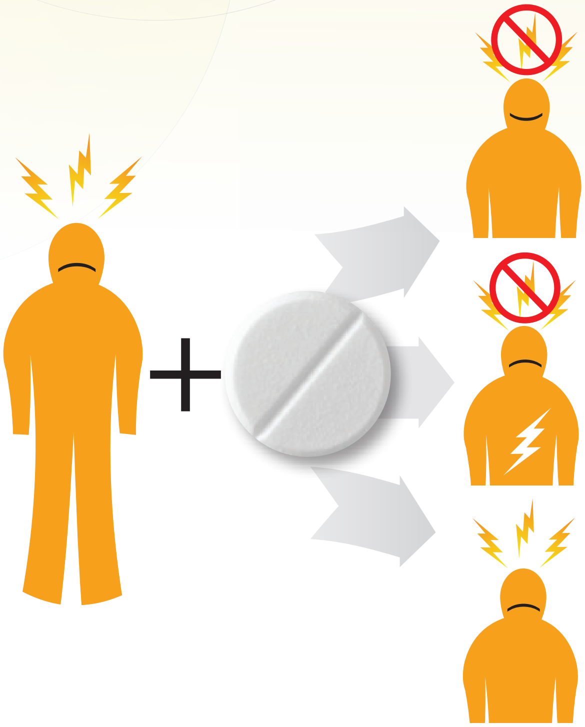
[2] The Cochrane Collaboration: Glossary, http://www.cochrane.org/glossary/. Accessed June 6, 2013.

> “The average patient isn’t the individual patient.”
>
> **Dr. Robert Dubois,**
> **Chief Science Officer,**
> **National Pharmaceutical Council**



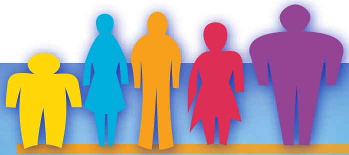
Heterogeneity and Individual Treatment Effects (Continued)

We see these individual treatment effects all the time. For example, aspirin is commonly used to treat headaches. For some people, it works well and without side effects. For other people, it cures the headache but causes stomach upset. And for certain people, aspirin doesn’t cause an upset stomach, but it also doesn’t make a dent in the pain.



Because different patients can have very different responses when it comes to Treatment A vs. Treatment B, the treatment that’s best for most patients may not be the one that’s right for you.

Within this booklet, we refer to differences in how individuals respond to treatments as **“heterogeneity”** and **“individual treatment effects.”** Individual differences can have an important impact on your health, from finding the right treatment to making sure the right treatment is covered under your health insurance plan.



Being Your Own Advocate

Later in this booklet, you'll learn about the challenges of getting the right care in the face of individual treatment responses. Below are some important conversation starters to help you and your health care provider achieve the best possible health outcome for you.

As you read through this resource, you'll see that many questions about individual treatment effects remain unanswered, but there are opportunities for patients to use the available knowledge to improve their care.

It is important for patients to discuss the current state of research with their health care providers and caregivers when they weigh medical decisions. Patients, caregivers and advocates can play a key role in bringing individual treatment effects to the forefront of the conversation. Patients should feel comfortable raising concerns about the possibility they won't respond to a treatment, discussing potential side effects, or explaining different preferences for outcomes with their health care providers. Having these conversations can make it easier for patients and those involved in their care to work together to determine the best strategy for dealing with treatment variations.

Here are some questions patients and caregivers can ask to start the discussion:

- ✔ What are my treatment options and what are the potential benefits and risks?
- ✔ Do any of my personal preferences (e.g., lifestyle, work capabilities, health outcomes) limit my treatment options?
- ✔ Am I at high or low risk of having a condition develop or worsen? How does that affect your treatment recommendation?
- ✔ What kinds of side effects could I experience with each treatment option?
- ✔ Given my personal characteristics (e.g., age, gender, race, etc.) and health history, do you think I could have an unexpected response to the treatment you are recommending? Has there been any research into unanticipated responses for patients with my characteristics and condition? How different are patient responses to this treatment?
- ✔ If I don't respond to the therapy you are recommending, what would be the next steps in treating my condition?
- ✔ If I don't respond to this treatment, will my health insurance plan cover other options?
- ✔ What is likely to happen to me, given my characteristics, health condition(s) and personal preferences?

To make it easier for you to have this conversation, you can bring this checklist of questions with you during your next visit to your health care provider. The checklist is available as a tear out card in the back of this booklet.

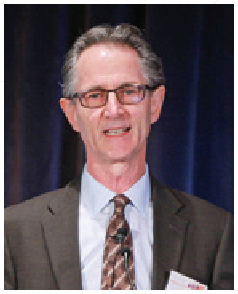
> "If we can get information into people's hands, then hopefully we can get to some better clinical outcomes."

Paul Martino,
SVP of Clinical Strategy
and Innovation, WellPoint

New Urgency in Understanding Individual Treatment Effects

> “Innovation is going to be driven by understanding patients are different.”

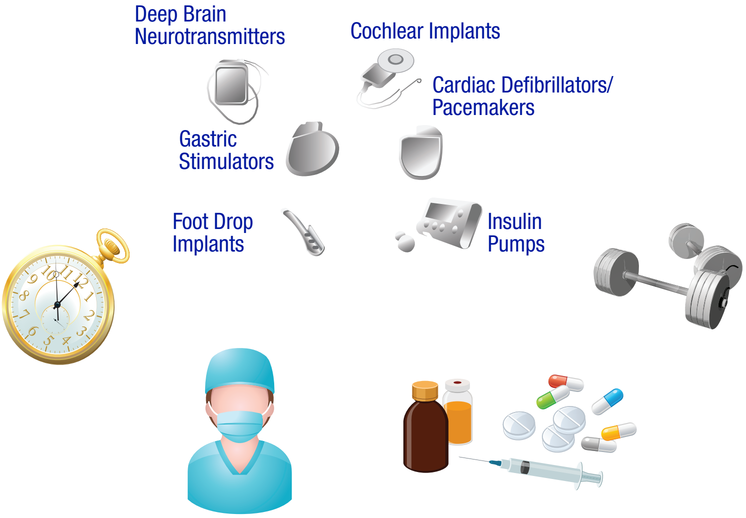
Dr. Joe Selby, Executive Director, Patient-Centered Outcomes Research Institute



Your individual needs have always been important, yet within the health care system there has always been a struggle—among researchers, medical professionals, health insurance companies, and others—to meet the needs of millions of people and still recognize the unique needs of each individual person.

As health care spending has risen over the years, the effort to both improve the quality of care and get spending under control has led to a growing public and private investment in comparative effectiveness research (CER), sometimes called “patient-centered outcomes research” (PCOR).

The goal of CER is to discover what treatments and interventions work “best.” At its most basic definition, CER involves comparing one treatment option against another treatment option. Examples include surgery or watchful waiting; using a medical device or exercising; or comparing one drug to another drug—there are any number of approaches that can be compared.



New Urgency in Understanding Individual Treatment Effects (Continued.)

According to the Patient-Centered Outcomes Research Institute (PCORI), CER "helps people and their caregivers make informed health care decisions." CER answers questions such as "given my personal characteristics, conditions and preferences, what should I expect will happen to me? What are my options and what are the potential benefits and harms of those options?"[3]

Much of the CER conducted in the United States will be funded and overseen by PCORI, which was established as an independent entity under the 2010 health care reform law. Although PCORI will be playing a leading role, organizations such as the Agency for Healthcare Research and Quality, the National Institutes of Health, academic institutions, and private payers also are conducting CER.

CER has the potential to significantly impact how we make medical decisions in the future. The question on everyone's mind is—will CER be done right? Will research take into account the need to understand different patient populations, be large enough to detect differences, and designed to identify unexpected responses? PCORI's leadership acknowledges that careful thinking about individual patient differences is important to their vision of developing "information [patients and the public] need to make decisions that reflect their desired health outcomes."[4]

At a November 2012 conference, *The Myth of Average: Why Individual Patient Differences Matter*, Myrl Weinberg of the National Health Council, Dr. David M. Kent of Tufts University and Dr. C. Daniel Mullins of the University of Maryland speak about patient variability and study findings.

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[3] Patient-Centered Outcomes Research Institute: Patient-Centered Outcomes Research, http://www.pcori.org/research-we-support/pcor/. Accessed June 26, 2013.

[4] Patient-Centered Outcomes Research Institute: Mission and Vision, http://pcori.org/about-us/mission-and-vision/. Accessed August 1, 2013.

Why Individual Treatment Effects Matter

What happens when you're not "average"? Because people are different in so many ways and have diverse characteristics, it may mean there isn't research available on patients who are similar to you. When that happens, it can be harder to know what treatment is right for you and it might be harder to access that treatment.

There are a few reasons for this. Medical research is great at determining how the "average" patient will respond to a treatment, but it may not always do a good job of helping you understand how you'll respond if you don't fall into that "average" group.

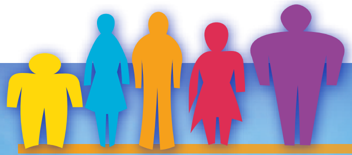
In other words, many research studies are designed assuming the world looks like this:

Applying the findings of that research to your personal needs may be tough if you happen to find yourself in this group:

If your health care provider is basing his or her recommendations only on how the "average" person fared on that treatment, you may not get the treatment that's right for you.

Second, because most health plans design their policies to meet the needs of the majority of people, those who are different—older or younger, or with different racial or ethnic backgrounds, for example—may have a difficult time getting other treatment options covered. Some health plans require patients to try the "average" therapy first before trying another treatment, even if it is not the best option. Many organizations that represent patients are concerned that comparative effectiveness research could be used to delay or block access to the right treatments for those patients who respond differently than the "average" patient.

> "When exploring treatment options in children diagnosed with bipolar disorder, it is important to remember each child is different, and may respond to different medications. Some children may need more than one medication to control their symptoms."
>
> **National Alliance on Mental Illness, Ask the Psychiatric Pharmacist #21.**



Detecting Differences

Health care providers see firsthand that patients who are similar and have a certain illness or condition may have very different reactions to a course of treatment. It can be difficult, however, for researchers to understand the causes of those differences and capture that kind of "real-world" information. Experts agree that in order to detect how different patients may react to different treatments, comparative effectiveness research (CER) studies have to:

Be large enough

Studying smaller groups of people may not reveal patterns. Addressing many patient characteristics in a study requires a very large group.

Potential solutions: As the use of electronic health records increases, large databases are being built to store this information. Having health information more readily available may allow more targeted questions to be answered.

Ask the right questions

Traditionally, research has not involved patients, except as study subjects. Most often, researchers who don't deal with the condition themselves decide what issues are most important to study. This can mean the factors that matter most to patients can be overlooked.

Potential solutions: Experts want to involve patients in research at the study design stage so patients can play a greater role in setting research priorities. When a patient's preferred health outcome—such as quality of life—is taken into account in medical decisions, patients are more likely to stick to their treatment plans. This type of patient involvement can improve health outcomes and potentially save money by reducing preventable hospital stays.

Study relevant populations

Deciding on treatments can be frustrating to patients when there is no evidence to show whether a treatment will work for them. For instance, only a handful of prescription drugs have been studied in large enough numbers of African-American women for researchers to draw any conclusions with certainty.

Potential solutions: Not all research studies can be large enough to effectively answer questions for every individual patient. When possible, researchers should design studies that take relevant subpopulations (a specific group of people within a study) into account.

> "I think we need to listen to the patient to hear what's most important so we spend their dollars most wisely."

Dr. C. Daniel Mullins, Professor, University of Maryland School of Pharmacy

> "From my perspective, we must look at patients from a wide lens even as we try to measure outcomes."

Dr. Sharon Allison-Ottey, Executive Director and Director of Health and Community Initiatives, The COSHAR Foundation

Keeping CER Focused on Patients

PCORI is incorporating the realities of individual patient treatment effects into how the organization funds research, noted PCORI Executive Director Dr. Joe Selby. All PCORI research applicants will be required to seek a wide spectrum of patients for their research and explain how they intend to study unexpected treatment responses in subpopulations. "It falls on us in conducting the science of the future, and particularly CER, to be attentive to those (individual patient) differences," Dr. Selby said.

Accounting for Individual Responses

"It's important to keep patients at the forefront of this research."

Dr. Ellen Sigal,
Chairperson and Founder,
Friends of Cancer Research

How exactly will you react to a specific medical treatment? The only way to know for certain is to try the therapy and see if it works.

But trial and error isn't always practical, particularly in cases of serious illness. Patients, physicians and researchers agree that in an ideal world, it would be possible to predict how individual patients would react to a treatment. Although medical research is making progress on that front, patients and health care providers still need better information to help them make decisions.

Breakthroughs in cancer treatment illustrate this issue well. Cancers, such as breast cancer, can have various genetic signatures that respond differently to treatments. Researchers are gaining a better understanding of how to best match treatments to those genetic signatures. But with only about five percent of cancer patients participating in clinical trials, it can be challenging to recruit diverse participants who can help researchers gain important insights into variations in treatment responses.

In addition to understanding a treatment's effectiveness, patients are particularly interested in understanding the potential side effects of various treatment options. Patients are in the best position to know what side effects they are willing to tolerate so they should be able to freely discuss with their health care providers the side effects and their potential impact on their personal and professional lives.

"Many patients do not benefit from the first drug they are offered in treatment. For example, 38 percent of depression patients, 50 percent of arthritis patients, 40 percent of asthma patients, and 43 percent of diabetic patients will not respond to initial treatment."

***The Case for Personalized Medicine*, 3rd Edition**

Denied for Being Different?

Health Plans and Coverage Challenges

What happens when your health plan only covers one treatment for your condition—and that treatment doesn't help you? Patients who don't respond, respond poorly, or experience side effects to therapies can find themselves paying higher out-of-pocket prices for additional options.

To balance the needs of many people with the needs of the individual, public and private insurers are looking to comparative effectiveness research (CER) to provide direction about what treatments offer the most promise for the majority of people and to understand and identify potential variations in treatment effects. Along with considering CER findings, the Centers for Medicare and Medicaid Services (CMS) is developing quality measures of care that balance health provider accountability with flexibility for patient care.

Dr. Patrick Conway, Chief Medical Officer, Centers for Medicare & Medicaid Services, speaks about the importance of measuring the quality of care for patients.

Yet many patients and caregivers fear CER could be used to deny access to treatments. People who have conditions like depression, where treatment responses can vary greatly, know firsthand that a one-size-fits-all approach to medical treatment can be very harmful to patients.

Advocates for patients say that policymakers at CMS as well as private insurers need to provide options for physicians and patients when a therapy doesn't work. Better research that is designed to show how widespread individual treatment responses are can guide coverage decisions that best serve patients.

What can you do? If you are looking for a health plan, here are some questions you will want to consider:

- How much flexibility does the insurance plan have for my health condition(s)?
- What is the limited list of drugs the plan will cover? This limited list is known as a "formulary." If you take medications for a chronic illness, such as high blood pressure, asthma, or diabetes, be sure those medicines are on the formulary before you select that plan. If they aren't, you could be expected to switch to different medications or pay the cost yourself.
  - Does the health plan have to approve my medicine before they will pay for me to have it (also called "prior authorization")?
  - Will I need to try several treatments before getting the one that works for me?
- How many treatments are covered?
- Will my health plan require a co-payment for my prescriptions? Many plans will have three or even four levels, or "tiers," of co-payments that apply to different medicines. Find out what co-payment level applies to each medication you are taking by calling the plan or looking in the materials you received from them.
- Is the appeals process easy for patients like me to use?

> “We need to create and we want to create clinically nuanced policies. We can only go so far as the evidence allows us to go.”

Dr. Lewis G. Sandy,
SVP, Clinical Advancement,
UnitedHealth Group

Making Sound Coverage Decisions

The National Pharmaceutical Council is developing guidelines to help health insurers decide when greater flexibility is needed to deal with individual treatment responses. The tool considers the following factors:

- How easy is it to predict individual responses to treatment for a condition?
    - How predictable is the response?
    - Is the physician the only one in a position to predict responses?
    - Can the payer also predict diverse responses to the treatment through lab results or the presence of other conditions in the patient?
    - Are individual responses completely unpredictable?
    - What are the consequences of not getting the optimal treatment at the start? Will there be another chance to get it right, or will a delay in finding the right treatment cause serious harm?
- How much flexibility does the insurance plan have for that condition?
    - How many treatments are covered?
    - Are there co-pays?
    - Is prior authorization required?
    - Does the patient need to try several treatments before getting the one that works for him or her?
    - Is the appeals process easy for patients to use?

Using this information, the tool assesses whether the amount of flexibility needed by the health care professional lines up with the health insurance plan’s ability to make changes.

Asking Your Health Care Provider About Individual Treatment Effects

To make it easier for you to have a conversation about individual treatment effects, you can bring this checklist of questions with you during your next visit to your health care provider.

- ✔ What are my treatment options and what are the potential benefits and risks?
- ✔ Do any of my personal preferences (e.g., lifestyle, work capabilities, health outcomes) limit my treatment options?
- ✔ Am I at high or low risk of having a condition develop or worsen? How does that affect your treatment recommendation?
- ✔ What kinds of side effects could I experience with each treatment option?
- ✔ Given my personal characteristics (e.g., age, gender, race, etc.) and health history, do you think I could have an unexpected response to the treatment you are recommending? Has there been any research into unanticipated responses for patients with my characteristics and condition? How different are patient responses to this treatment?
- ✔ If I don’t respond to the therapy you are recommending, what would be the next steps in treating my condition?
- ✔ If I don’t respond to this treatment, will my health insurance plan cover other options?
- ✔ What is likely to happen to me, given my characteristics, health condition(s) and personal preferences?

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