The Promise and Limits of "Personalized Medicine"

An Introduction to *n=1*

by Daniel J. Bressler, MD, FACP

THE TERM "personalized medicine" has come to mean medical care organized around specific molecular biomarkers. It is applied most commonly in oncology as a description of treatments adapted to cancer-specific mutations. Some prominent examples include the use of trastuzumab (Herceptin) targeted to those breast cancer patients whose cancer overexpresses the HER2 growth factor receptor; the use of cetuximab (Erbitux) restricted to those metastatic colorectal cancer patients whose tissue KRAS gene is wild-type (i.e. unmutated); and mutational subtyping of CML in order to determine whether treatment with tyrosine kinase inhibitors will be effective. In the field of infectious diseases it has found multiple applications, such as guidance for the use of the anti-HIV drug abacavir for patients who have tested negative for the gene variant HLA B*5701. In cardiovascular medicine, warfarin dosing can be refined by knowledge of the genes that code for its metabolism. New therapeutic and diagnostic applications are coming thick and fast in most branches of medicine, from psychiatry to transplant surgery.

The slogan of personalized medicine is "the right drug at the right dose for the right patient." This phrase can be interpreted as a biologically slanted resurrection of the corny old Oslerian proverb that many of us were exposed to in medical school: "It is more important to know what sort of person has the disease than it is to know what sort of disease the person has." Through pharmacogenomics, we can ask what sort of Cytochrome P450 variant is present in the patient with chronic pain who is about to be prescribed pregabalin (Lyrica.) We might inquire as to the genetically determined clopidogrel (Plavix) metabolism in the patient with a recent stent. And with molecularly targeted therapy, we seek to know what sort of alteration of the tissue-specific "genetic self" has given rise to the patient's cancer.

The variable "n" is, of course, the number of subjects in an experimental trial. It is a principal determinant in calculating the statistical power of an experiment. In general, the greater the n, the more compelling the study's conclusions. The gold standard of evidence-based medicine is the large, randomized, placebo-controlled clinical

n = 1

Science is based on statistics
The scorecard when all's said and done
But all of its sums and logistics
Stumble on n = 1

You give me the law of the average
I say that you've barely begun
Does wetness make it a beverage?
Uniqueness makes n = 1

Seemingly sameness distinguished
Identical twins? There are none
Differences can't be extinguished
It all boils down to n = 1

You tell me the future's genetic
Sequencing our latest top gun
But a lived life is epigenetic
It turns out that n = 1

We can measure the serum albumin
With a certainty certain to stun
But how do you measure a human
When each person's n = 1?

We aim to be so formulaic
Our flow charts show how it is done
But a person is rare and mosaic
Each life proves that n = 1

A cookbook's an adequate master
When baking a cake or a bun
But recipes lead to disaster
For a person whose n = 1

Can I leave you with some kind of moral
A word for your daughter and son?
You must master your field without quarrel
Just remember that n = 1

"It is more important to know what sort of person has the disease than it is to know what sort of disease the person has."

trial. The large refers to a high "n."

When one goes from a clinical study to the clinic, however, n is always equal to 1. The fine print of a clinical study is made up of the inclusion and exclusion criteria. These are necessary for practical and safety purposes. But they limit the strict applicability of conclusions of the study to those patients who meet study criteria. And even among those patients, we can never be sure (only statistically inclined) that the reasoning of the study applies to the patient sitting in front of us. If the patient is somehow a perfect amalgam of the study group, we might be able to say that she has a 70% chance of a beneficial response and a 20% chance of serious side effects, just as has been shown in the clinical trial. But such a claim is ludicrous. Patients are not statistical amalgams. The patient will either have the response or she won't. She'll either have the side effects or she won't. A patient doesn't live in the abstract world of probabilities. She lives in the world of flesh and bones where outcomes are actualities rather than likelihoods.

So, yes, large, randomized, placebo-controlled trials do give us protocols to follow. And, yes, the new molecularly based diagnostics and therapeutics will help make those protocols more precise. But even so, such protocols give us only starting places in the iterative process that is clinical medicine. They will refine therapies analogously to how culture-and-sensitivity techniques have refined our treatment of infections. Although a significant achievement, this refinement will not end the ongoing challenges in oncology, neurology, adverse drug reactions, or any other field of medicine.

As important as all these genetically and metabolically directed therapies are and will increasingly become, I like to believe that we all would be better off reserving the term "personalized medicine" for a kind of clinical relationship that is both molecularly specific and humanistically specific. The Oslerian "sort of patient who has a disease" cannot be adequately summarized in a proteomic signature or metabolic portrait no matter how detailed. It leaves out what makes us human as opposed to what makes us complex biological composites. What it leaves out is the essence of our humanity: our beliefs, our preferences, our fears, our goals, and our hopes. It leaves out where we come from, who we love, what we despise, and why we want to get better.

This little poem, *n=1*, is an attempt to draw the distinction between medicine as an inductive science that produces its conclusions from large groups and medicine as an application of that science to the life of an individual, idiosyncratic, and singular person. It is a reminder to myself, and perhaps to you, that being a practicing clinician will forever be a balancing act between these two medicines. SDP

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