

Is “Precision Medicine” Ready to Use in Primary Care Practice?

No: It Is Barely Ready for Testing

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Precision medicine has, at times, been vaguely defined, or used to convey the age-old concept of tailoring tests and treatments to an individual patient. To be a truly new paradigm, however, a more meaningful definition must signify the use of -omic (e.g., genomic, proteomic, epigenomic) markers to assign therapies to individual patients at the individual level. As a hypothetical example, precision medicine in hypertension would mean some genetic (or -omic) tests that recommend calcium channel blockers, thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, or some unique combination of these; specific starting doses; and even no therapy (i.e., observation) based on an individual model of risk reduction and harms. This idea would be truly novel; however, in primary care, there is no single example of such a precise test in practice or in development.

Instead, physicians settle for crude approximations to precision medicine, such as the use of genetic tests to define groups that benefit from certain therapies. In 2017, the science is with groups, not individual persons; for example, all women with germline *BRCA1* mutations or all persons with lung cancer and epidermal growth factor receptor activating mutations. Conceptually, these groups are no different from all persons with chronic obstructive pulmonary disease and forced expiratory volume in one second of less than 1 L, or all those with ejection fractions less than 35%. Rather than clinical, laboratory, or physiologic findings defining cohorts, genetics are used to define the groups. However, all the necessary rules of evidence-based medicine still apply, including risk derivation,



This is one in a series of pro/con editorials discussing controversial issues in family medicine.

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validation, and the need to prove important clinical benefits in a randomized trial when these tests are used.

Even accepting a definition of precision medicine based on groups of patients (not individuals), we believe it is clear that success in primary care has been absent. Genotypically guided warfarin (Coumadin) dosing is no better than clinically guided dosing in a meta-analysis of nine randomized studies.¹ Although the cytochrome P219C variant was thought to predict clopidogrel (Plavix) responsiveness, the best meta-analyses on the topic failed to validate this finding.^{2,3} In the only randomized controlled trial of a pharmacogenomic test to guide antidepressant selection, there were no statistically significant benefits in depression remission or symptom score at 10 weeks compared with usual care.⁴ Although some trials have shown genetic variants predict responsiveness to certain antihypertensives, we are not aware of any studies that show up-front testing for these variants and that tailored therapy is superior to current clinical practice. For this reason, it is not surprising that physicians treating hypertension start with a trial of a thiazide diuretic and not a far more costly genetic test.

Precision medicine is sometimes used to describe genetic tests that can lead to preventive care. Perhaps the best-known example for this is the use of *BRCA1* mutational testing to inform a person of cancer risk, potentially leading to prophylactic

mastectomy or oophorectomy. Here again, individual nuance rarely enters the discussion. Although there are *BRCA1* mutations that definitively predict high risk when combined with a family history of cancer, there are many mutations of unknown significance or those arising from unremarkable histories, in which the real risk and real benefits of prophylactic surgery are not well known. Consequently, the U.S. Preventive Services Task Force advises considering *BRCA1* screening in women with a strong family history and not those without it.⁵ Thus, the clinical story (family history) remains the backbone of the recommendation, and not the genetics (screening irrespective of family history).

In 2017, the only real precision medicine that a primary physician needs can be found in the examination room. Was the patient symptomatic or was this an incidental finding? How did the problem start? What does the patient value? How willing is the patient to accept the harms of therapy for the presumed potential benefits? How is the patient doing on therapy?

Precision medicine is ultimately only a tool, and just as it might be used to facilitate better outcomes, if adopted prematurely, it may paradoxically increase inappropriate care. Therefore, primary care physicians must wait for carefully conducted randomized studies to demonstrate benefits before embracing it. Moreover, physicians must remember that there have yet to be any examples of true precision medicine—the use of a therapy at an individual level. Although we look forward to this day, we believe the bar for such practices must be proof of improved outcomes over current treatment strategies. Primary care physicians should remember that what remains

most important is not the label precision medicine, but the evidence behind it.

EDITOR'S NOTE: What is precision medicine? Some define it narrowly as “genomic medicine,” or as tailoring diagnosis and treatment based on a patient’s genetic information. If so, then like Drs. Prasad and Obley, I think that it has largely not yet proved its potential to improve clinical outcomes. But some, like Dr. Feero, define it broadly as taking into account all relevant variables about an individual patient, and using this information to tailor treatment. If so, then that seems like a long-standing principle of care, with good evidence of improved outcomes. The degree of controversy over precision medicine’s value hinges on the definition used—genomic/molecular medicine vs. individualized care (with or without genetic information). We hope that these pro/con editorials shed light on a topic of heightened interest in this day of home DNA kits, and counter some of the potential hype of unfulfilled genetic solutions for age-old clinical problems.—Jay Siwek, MD, Editor, *American Family Physician*

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