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# Yaffe Award Lecture

## The Dawn of Pediatric Personalized Therapeutics

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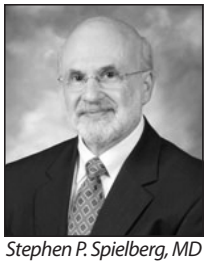
*Stephen P. Spielberg, MD*

It is a great honor for me to have been awarded the Sumner Yaffe Lifetime Achievement Award in Pediatric Clinical Pharmacology. Dr. Yaffe has been a lifelong mentor and colleague, a true definer of a discipline, creator of the Pediatric Pharmacology Research Units (PPRU) sponsored by the NICHD, and a dear friend. I am tremendously grateful to the PPAG for honoring me with this award in his name.

The last years have been important ones for pediatric therapeutics. The scientific basis has been driven by huge advances in pediatric clinical pharmacology, fundamental understanding of the ontogeny of drug disposition and of drug response. United States legislation including the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have changed the drug development process, leading to new knowledge about the safe, effective use of medicines in children. Research networks including the Pediatric Pharmacology Research Units (PPRUs), the Children's Oncology Group, and now the Clinical and Translational Science Award (CTSA) network have increased pediatric investigative activities throughout the country. The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have both played critical roles, with the FDA Critical Path initiative in many ways reflecting scientific thinking about translational medicine driving the NIH CTSAs. Pediatric research incentives and requirements now have been implemented in Europe under the European Medicines Evaluation Agency (EMEA), and the International Conference on Harmonization process has led to harmonization of science, education, and much of regulatory activities among the United States, Europe, and Japan. A new focus on children living in the developing world (really the majority of the world's children) has led to a Pediatric Essential Drug List from the World Health Organization, along with a new "Make Medicines Child-Sized" initiative. Organizations such as the Gates and Clinton Foundations have also focused on the health needs of children throughout the world. All of these activities have engendered a sense of hope for the future of the world's children, and also recognition of the enormous challenges ahead to:1) prevent disease and incapacity; 2)address neglected diseases afflicting the majority of the world's children; 3)develop new knowledge to more effectively understand and treat diseases of the developed and developing world; and 4)

**ABBREVIATIONS** ADRs, adverse drug reactions; CTSA, Clinical and Translational Science Award; CYP2D6, Cytochrome P2D6 System; CYP2D9, Cytochrome P2D9 System; EMEA, European Medicines Evaluation Agency; FDA, Food and Drug Administration; GENDEP, Genome Based Therapeutic Drugs for Depression; GWAS, whole genome association studies; MDD, major depressive disorder; NICHD, National Institute of Child Health and Human Development; NIH, National Institutes of Health; PPRU, Pediatric Pharmacology Research Units; SSRIs, selective serotonin reuptake inhibitors

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assure access of all children to advances in medical science and medical treatment, and equally important, to live in a world of social, political, and economic stability.

Perhaps the most exciting scientific advances of the last years have been in the realm of genomics, insights gained literally revolutionizing the way in which we think about disease, diagnosis, and treatment. While we really should not be surprised, with advances in knowledge, much of our previous understanding of biology will have to be changed, and things are turning out not to be as straight forward with respect to organization, expression, and function of our genome as we might have imaged. As we explore the human genome, long standing recognition of human heterogeneity and variability becomes all the more apparent. Claude Bernard, the great 19th century physiologist recognized human idiosyncrasy long ago.

> "A physician is by no means a physician to living beings in general, not even physician to the human race, but rather, physician to a human individual, and still more physician to an individual in certain morbid conditions peculiar to himself and forming what is called his idiosyncrasy."
>
> Claude Bernard,
> *Introduction to Experimental Medicine*, 1865

Today, we develop ever more targeted medicines, their chemistry designed to interact specifically with human recombinantly expressed targets. Given that we know just how much heterogeneity exists throughout the genome, the questions we should be (but often have not been) asking about a target of a new drug include: 1) Does the target have genetic variants in the population? 2) Are variants likely to alter the effectiveness of the drug? 3) What percentage of the population expresses the variants, and how might this impact the percentage of the population likely to benefit? 4) What is the relevance of the target in the metabolic 'economy' of complex pathways we are trying to impact? 5) Are there alternative/rescue/susceptibility/resilience pathways that may lead to 'escape' from impacting the target, and how do these pathways vary in the population?

For so many drugs currently on the market, 40%-80% response (sometimes less) in the population are not uncommon; only rarely will a medicine work in nearly all patients. This may be due to imprecision in diagnosis; in other words, the patient's syndrome is not related to the target of the drug. It could result from inadequate clinical diagnosis (description of the patient's phenotype and resultant treatment of patients with heterogeneous diseases we lump together under a diagnostic category). It could result from a genetic variant in the target for the drug leading to lack of efficacy. It could result from pharmacogenetic variants in drug metabolism or transport, altering the kinetics of the drug, and making standard doses ineffective (or toxic). And, not all variation is genetic, but we need to think about developmental, environmental, dietary, drug-drug and drug-disease interactions and adherence as sources of variability. Traditionally, population variability was "accepted" but not addressed, and drugs were introduced in the hope of being "blockbusters" used by a large population of patients, and if some did not benefit (or developed unexpected side effects), this was unpredictable. We are now moving into a transition period where biomarkers of variability, many based on genomic technologies, will increasingly aid in diagnostic precision, and in selecting medicines most likely to benefit and least likely to harm a specific patient. The era of personalized therapeutics is just beginning, but the promise of an integrated diagnostic/therapeutic approach to individualizing therapeutics holds the opportunity for physicians and patients of establishing individualized benefit: risk, improved health outcomes, and ultimately an increased "value proposition" for pharmacotherapy for the individual and for society as a whole.

Before looking in depth at one pediatric therapeutic area as an example, it is worth pointing out an increasing dynamic tension between "comparative effectiveness studies" and "personalized medicine". The key question that needs to be addressed to rise above the politics and focus investigative activities that reflect the realities of human biology and therapeutics is this: In a genetically and environmentally heterogeneous human population with genetically and environmentally heterogeneous diseases (often lumped together under diagnostic categories), are standard comparative efficacy/effectiveness studies and population average outcomes an appropriate approach to improving individual and population health- and cost-benefit? Put dif-

ferently: Should we be thinking about DRUG OF CHOICE FOR WHOM? Standard comparative effectiveness studies might "demonstrate" no added benefit of a new, more expensive medication over an older generic one on a population basis, but fail to detect those who could optimally benefit from one or the other. I believe we can creatively integrate the best of comparative effectiveness science and genomic science to achieve optimized therapeutic outcomes for each patient, and in so doing, optimize overall health- and cost-effectiveness of therapy. This will require a paradigm shift in effectiveness research, but human diversity in disease causation and response to therapy demands incorporation of individual outcomes and use of biomarkers of efficacy and adverse effects into study designs, and hence to guide rational and effective therapeutics in the real world.

It is also important, before focusing on advances in pharmacogenomics and how they will contribute to improve therapeutics, to at least mention that personalized medicine also MUST address issues of patient adherence and the therapeutic relationship between patient and health care provider. In a country where a high percentage of prescriptions are not filled, and many of those that are filled are not taken as prescribed, we have a huge challenge regarding optimizing the social and relational interactions that lead to positive pharmacotherapy. For children, this also includes providing optimal formulations of medicines that enhance administration, accurate and flexible dosing, and long-term adherence. For us all (we are all patients at some time), and for those caring for the sick, somehow we need to re-think the issues of "time and talk", the core of establishing therapeutic relationships. While this is a topic for another article, it is a discussion in which we must engage, and urgently, in our training programs, and in the organization of health care delivery. In summary, optimal personalized therapeutics requires: medicines and formulations that optimize accurate, flexible, palatable, adherent use; personalized care and development of a therapeutic relationship for each patient; and biomarkers to help optimize selection of the right drug for the right patient at the right dose.

Using the example of antidepressant treatment of depression in children, I will try to examine some of the features of optimized personalized medicine, from clinical diagnosis through genomic diagnostics, as well as pointing out some hurdles and challenges we face as we enter an increasingly genomic era. While precision in establishing a patient's "phenotype" may seem to be more difficult for depression than for some other conditions, in fact, the issue of phenotypic specificity is crucial to all aspects of medicine. No matter how good a biomarker, genomic or other, may be in predicting outcomes of pharmacotherapy, if applied to a mixed, heterogeneous group of patients, clinical trials and clinical care will fail. True personalized therapeutics will require advances in genomic science, but as we will see in the example of depression, improvements in accurate patient description as well. Clinical diagnosis and the relationship between patient and caregiver will remain the heart of individualized care. Furthermore, electronic medical records will not save us, unless the clinical content, precision of clinical description, standardization of terminology is not markedly enhanced, and linkage enabled, with all appropriate patient confidentiality safeguards, to genomic information. To the extent that "diagnosis" is linked more to billing and codes that do not reflect complex biology, we risk garbage in and garbage out. On the other hand, having rich, detailed phenotypic data and genomic information in formats allowing both for optimized research and patient care will clearly help advance medicine.

Recently, there was an excellence "point-counterpoint" discussion about the safety and efficacy of antidepressants in children and adolescents with depression.[1,2] Major depressive disorder (MDD) is a potentially life-threatening disease, and its management, pharmacologic and otherwise, remains controversial. Recent studies of selective serotonin reuptake inhibitors (SSRIs), many done by industry under the Best Pharmaceuticals for Children Act and written requests from FDA, have sadly added additional confusion to the field.

With respect to efficacy, two carefully conducted trials 7 years apart by the National Institute of Mental Health clearly demonstrated the issue of efficacy of fluoxetine in depression in children and adolescents, with placebo responses around 35% and drug responses around 60%.[1] In most of the subsequent industry studies (save for one additional study of industry-sponsored study of fluoxetine), the studies "failed to show efficacy".

However, the studies failed NOT because of a decrease in drug effect, but rather because of a very high placebo response rate, often in the mid-50% range. Most of the studies were small; approximately 200 total patients, half on placebo, and, to meet the time requirements for patent expiry, had to be done in a very tight time frame. It appears likely that the *studies*, rather the *drugs*, failed, perhaps due to entry criteria (mis-diagnosis of MDD and entry of patients with milder mood disturbance), and other study flaws.

From the perspective of adverse drug reactions (ADRs), the issue of suicidal ideation associated with antidepressant therapy has been raised. There is a need for much better ways to monitor and assess suicidal ideation, and no patients in any of the studies actually attempted suicide. Labeling changes, congressional hearings, and associated publicity created the overall impression, however, that SSRIs may not be effective in management of young patients with depression, and that risk of suicidal ideation in younger patients makes the benefit:risk of using the medicines questionable. Concurrent with the publicity, there has been a decreased use of antidepressant drugs in the pediatric population, and a comparable increase in completed suicides.[3] While causality is uncertain, the epidemiologic trend is sobering, and many of my pediatric and pediatric psychiatry colleagues now find it increasingly difficult to use these medicines in their patients because of the adverse publicity.

Given all this, what is needed for the future, both for clinical trials, but more importantly for patients suffering with MDD? Assay sensitivity in depression studies has long been a problem in adult and pediatric trials.[4,5] Repeated studies of the same drug, seemingly similar in design, often yield conflicting results. This may be due to our inability to define, with adequate precision, the condition we are attempting to treat, the "phenotype" or "diagnosis". The current state of the art in clinical diagnosis, emphasizing the need for accurate ascertainment of phenotype, is thoughtfully discussed by Preskorn.[6] The diagnostic process requires expertise, collection of detailed information about the patient's condition, and perhaps most critically, time. The shortage of physicians well-trained in psychiatric diagnosis, and time pressures clearly are impeding care for patients in need. Diagnostic specificity may be all the more difficult in pediatric and adolescent patients, and clinical measures of diagnosis and outcome inconsistently applied among clinicians, investigators, and site. The wide range of placebo responses among studies, from 35%-60% highlights our lack of diagnostic precision.

High placebo response is common in most depression trials – many patients do not appear to "need" drugs, although they may benefit from the overall "therapeutic setting". Some patients might not really have the condition we think we are treating – i.e., MDD. Some may have other mood disorders likely to spontaneously improve ("transient depression of adolescence"), and teenagers, in particular, may have mood swings as part of maturation that, if we had better phenotypic and genotypic markers for MDD, we could separate out and avoid drug exposure. The clinical perspective also suggests that it is likely that we may be "over treating" patients who are not likely to need or benefit from a specific intervention. On the other hand, few trials of antidepressants achieve more than 60% benefit. Thus, there are patients suffering from depression who are not helped by a specific drug. One might ask whether they would benefit from a different drug class – see below. Since clinicians will be faced with patients who present with varying mood disorders, they need improved tools for differentiating among those who truly need pharmacotherapy, and those who might be resistant to pharmacotherapy with one or another compound or class of drug.

Improvement in benefit to risk also needs to address ADRs. For example, there are data suggesting increased risk of mania in bipolar patients treated with SSRI or tricyclic antidepressants.[6] If a patient with bipolar disease presents with depression, and the diagnosis of bipolar disease is not made, they may be at increased risk of "activation" side effects if treated with antidepressants. Similarly, some patients may indeed be at increased risk for drug-mediated suicidal ideation; in the small trials in pediatric patients, one or two of 100 patients in drug treated groups resulted in a "finding" of increase suicidal ideation risk. If we had better phenotypic (clinical) markers of bipolar disease, and other biomarkers of bipolar diagnosis and predictors of suicidal ideation risk, we could better target use of SSRIs and other antidepressant to optimize individual benefit to risk.

There are hints beginning to emerge of the

future approaches to determining the right treatment for the right patient. Metabolism by polymorphic enzymes, such as CYP2D6 and CYP2C9, can modify half-life of many antidepressants, and have the potential to alter efficacy and dose- (exposure-) related side effects.[6] Recent studies of polymorphisms in serotonin and norepinephrine targets of antidepressants suggest altered likelihood of successful treatment with one or another drug class based on genotype.[7-11] If we can distinguish patients more likely to benefit from an SSRI, a serotonin-norepinephrine reuptake inhibitor, or other drugs, or who will most likely benefit from psychotherapy (also likely to be modified by both genetic, environment, and developmental factors), we may be able to improve the odds of a beneficial outcome. It is likely that multiple genetic markers will modify outcomes, and genome-controlled trials will contribute to our understanding of the utility of such approaches in the selection of the right treatment for the right patient. Our current therapeutic armamentarium is limited with respect to transmitter targets, and to adequately help all patients, we will need new classes of medicines or combinations of medicines, cognitive behavioral and other "talk" therapies to improve the lives of patients whose condition is resistant to current interventions. Similarly, if we have markers enabling us to diagnose bipolar disease first presenting with depression, we can avoid potentially hazardous therapy and treat these patients with the right medications.

An interesting example of interaction among therapeutic modalities was recently published by Walkup et al.[12] A comparative study of placebo, an SSRI, and cognitive behavioral therapy was conducted in children with major social phobias/anxiety disorders. Targeted end points were achieved in 23.7% in the placebo group, 54.9% of those receiving an SSRI, and 58.7% of those in the cognitive behavioral therapy group. Both the SSRI and behavioral therapy were statistically significant when compared to placebo, and the two interventions did not differ from each other. A superficial comparative view would argue the two modalities are "the same", and from a cost point of view, the "cheapest" should be the treatment of choice. Looking further at the data, however, the SSRI arm achieved benefit more rapidly, and in an arm including *both* the SSRI and behavioral intervention, over 80% of patients improved. This could be due to synergy between the two treatments, or that some in either arm who did not respond to that treatment would respond to the alternate therapy. Additional studies, if confirmatory, and perhaps with designs allowing for the treatment of those who failed one arm with the alternative therapy will be important in defining with increased precision those patients most likely to benefit from one or another or both treatments.

An FDA review of suicidal ideation suggests possible age dependence in risk.[13] Development and ontogenic interactions with drugs in the central nervous system certainly is of concern, both with respect to pathogenesis of disease and the response to interventions. However, the precision of our ability to measure "suicidal ideation" in children and adolescents is uncertain, and the apparent age dependence may be related as much to the diagnostic and clinical trial tools we use, and how they are applied by individual investigators, as to actual drug effects. It is vital that we improve diagnostic precision for adverse effects as well as efficacy. Here, too, there is the opportunity to modify individual benefit to risk using predictive markers of risk. Efforts are underway to look for genomic markers associated with suicidal ideation risk.[14]

It cannot be stressed enough that both improved clinical diagnosis as well genomic and other biomarkers will be needed, that single genomic tests are unlikely to answer complex predictive questions, and that extensive validation of new approaches will need to be done. Outcomes of complex conditions and responses to complex therapies require a thoughtful integration of clinical medicine, genomics, genetics, and understanding of growth and development in children. Gene-gene interactions (epistasis) and genetic penetrance, gene-environment interactions, epigenetics, and development all play roles.[15,16] Many whole genome association studies (GWAS), to date, have found highly statistically significant associations between genomic markers and clinical conditions. However, many of the markers account for only a small percent of clinical variability (i.e., have very low penetrance) and GWAS currently are only able to detect variants expressed in 5% of the population. We will need to capture more rare genomic variants with higher predictive relevance, and analyze the consequences of

epistasis among multiple loci that will shape susceptibility/resilience to disease and modify outcomes of therapy. Genomic technologies are changing constantly, and we need to be prepared both for some "false starts" as well as markedly enhanced insights into genomic organization and expression over the coming years. All this will require a radical new approach to information acquisition and utilization, and interpretation on both the genomic and clinical side. There is urgent need to improve physicians' sophistication and skillful use of genomic data in the context of complex clinical syndromes, both for diagnosis and treatment. While the majority of physicians are convinced of the importance of genomics in transforming our understanding of health and disease, the vast majority feel ill-prepared to understand much less implement genomic and pharmacogenomic thinking into their practices. Equally important will be the creation and implementation of national and international networks of investigators who can advance this field. It will require cross-disciplinary cooperation among clinical pharmacologists, psychiatrists, pediatricians and developmental biologists, geneticists, bioinformaticists. The European "Genome Based Therapeutic Drugs for Depression – GENDEP" initiative is encouraging, while the loss of the NIMH Research Units in Pediatric Psychiatry is unfortunate indeed.

Finally, clinical care for patients with depression (and frankly all conditions) take *time*, thoughtful patient assessment, and close follow-up. Likewise, time is needed for primary care physicians and psychiatrists who care for patients with depression to learn about advances in personalized therapeutics, and to implement them skillfully in their practices. Time is not well-reimbursed in our current health care system, and scientific advances will have little impact without a concurrent change in practice. However, the current situation, one of confusion as to the value of medicines in treatment a life threatening condition, is unacceptable and is placing patients in need at risk. Change we must!

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