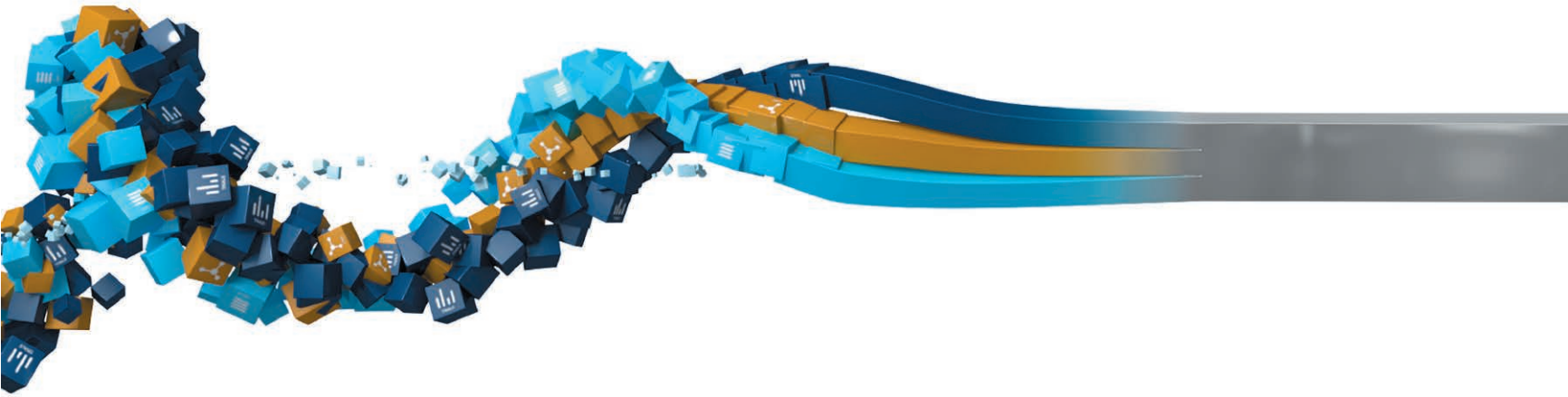

A New Disruptive Business Model: The Convergence of Precision Science, Precision Medicine, Precision Product Development, and Precision Commercialization

By **Gerald L. Messerschmidt, MD, FACP and Deborah Phippard, PhD**

THE TREATMENT of human disease states has historically been based in the medical knowledge available at the time of treatment.[1] Scientific knowledge is growing rapidly, with about 11,500 scientific articles published per working day (2018) appearing in >33,100 English language peer-reviewed journals.[2] Of these, medical science articles accounted for a large fraction (~32%). As shown in **Figure 1**, Medline indexed 952,919 citations in fiscal year 2020, equivalent to more than 3,665 peer-reviewed medical articles per working day in 2020.[3] How can those in healthcare possibly keep up with this rapidly growing medical knowledge?

Reviewing up-to-date literature and learning how to harness deep data for new drugs led the Precision Medicine Group to observe that a new business model was and is needed to harvest critical insights to increase the probability of success from product concept to approval. Consequently, new business *systems* are replacing older, less efficient, and obsolete therapeutic intervention trial designs. New business *structures* have been developed to maximize the precision of new product

development and success in humans with diseases requiring precision thinking. New *targets* are being identified and explored by thousands of scientists inventing new experimental therapeutics based on available precision knowledge.

Marhsall Nirenberg and Philip Leder cut through the complexity of the genome by deciphering the triplet nature of the genetic code while both were at the National Institutes of Health (NIH).[4,5] While Phil Leder was at the NIH and later at Harvard, he was a pioneer in introducing "precision" in the understanding of genes, proteins, the regulation of cellular products, and the diversity of antibody development.[6-10] The recognition of these precise biochemical and biophysical interactions between new products and new targets was termed "precision medicine" which has produced exacting therapies to improve the human condition.[11] More broadly, precision medicine (distinct from personalized medicine*) has come to refer to the way medical data and biomarkers can be used to determine treatments for patients based on population data. Today, scientific and medical precision is intimately converged in the work of the Precision Medicine Group to develop new systems, structures, and targets with clients (see **Case Study** inset[12]).

For some time, strategies to overcome the hurdles of developing new therapies had been designed to test for safety issues as early as possible and then select and refine candidates for efficacy. Our understanding of drug-human physiology interactions was poor and at times completely unknown with the result that safety issues were common among these early products, often small molecule pharmaceuticals, and efficacy often was not sufficient.

Commercialization

The other essential part of the model is commercialization. Precision medicine products tend to be costly to develop and many are associated with patients managing their disease or a returning to normal health. In this regard, Precision Value & Health supports rolling out precision medicine therapies, including cell and gene therapies, with campaigns that include medical communication, branding, advertising, and payer marketing. Naturally, life science innovators seek high prices in the market. The bar is high for evidence to support these price tags. Novel economic models are necessary to determine the value of treatments and, potentially, cures.

The Precision Medicine Group model specifically focuses on new advances, new data, and product functionality in human diseases that increase the probability of success. Optimally, Precision Medicine Group experts will be contacted early in the thinking required to move an experimental drug at time of conception to development with the goal of marketing approval. We champion changing the paradigm from previous product development pathways to more efficient and scientifically, medically and regulatory appropriate processes.

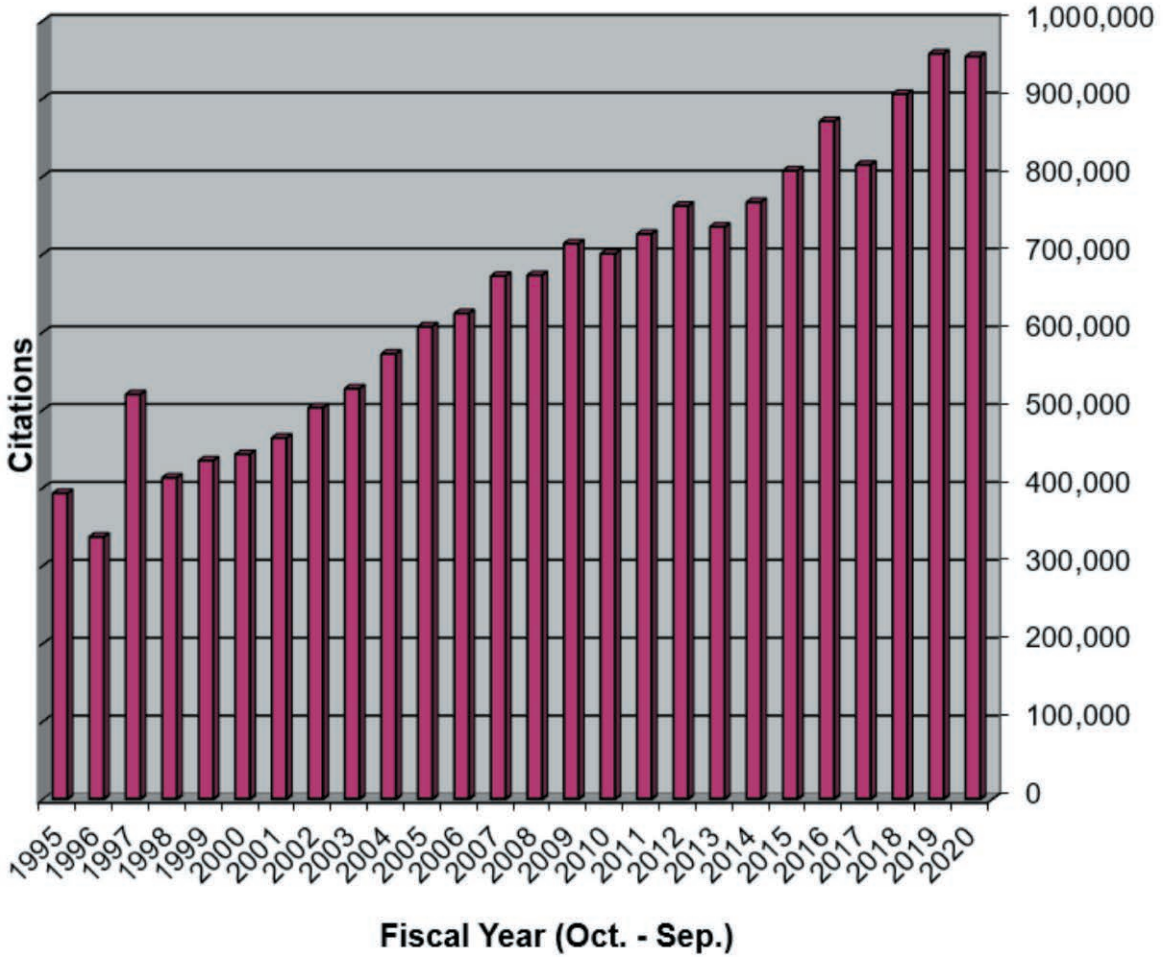

Figure 1: National Library of Medicine indexed citations fiscal years 1995-2020. Indexed citations are those citations selected for MEDLINE that have completed processing and indexing with current MeSH® (Medical Subject Headings®). Indexed citations have a status of MEDLINE. This number does not include OLDMEDLINE subset citations that are converted to MEDLINE status as part of the MeSH mapping project, effective FY 2007 forward.

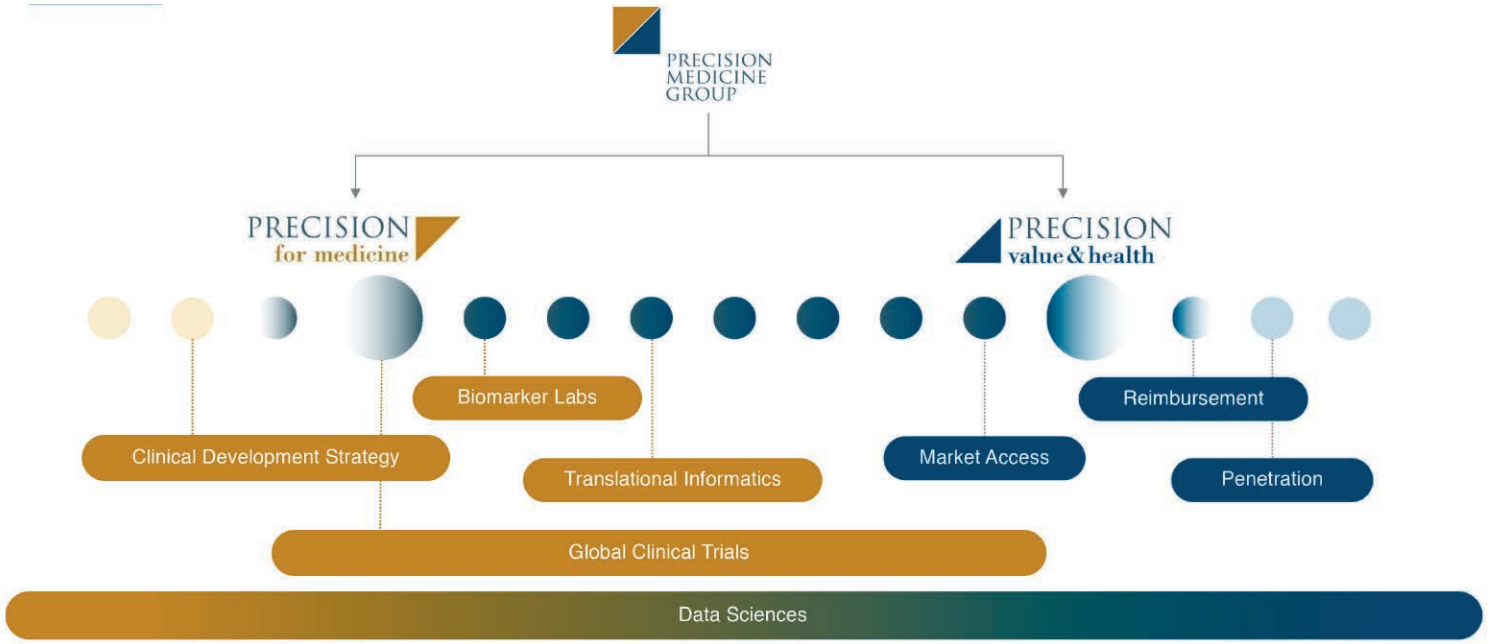

Figure 2: By converging research with development services then with commercialization strategies, efficiencies are gained in time, cost and likelihood of greater success.

"Though specific products are not designed within our company, their precise translation to the human environment and efficient development to gain rapid market approval is our expertise."

Today, our knowledge of biophysics and biochemistry is profoundly deeper and more precise in being explanatory and indicative of biophysical and biochemical interactions.

And while precision data that guides product development has never been more extensive and relevant, much remains unknown. Yet even more knowledge is needed to understand both normal and abnormal human physiological mechanisms and alterations in disease for drug development. In pace with the seemingly overwhelming accumulation of this knowledge (see **Figure 1**), we have been working to gain command of developing information for new safe and effective products.

Precision Medicine's Strategy for Targets

Genetic changes in coding genes have been a major focus of precision medicine since publication of the human genome and its subsequent refinements.[13]

A surprisingly low number of genes were identified from genetic sequencing, suggesting more than one mechanism is likely at work to create diversity. On the other hand, coding regions are easily measurable by various methods, such as surrogates (e.g., proteins) that were readily identified as pharmacologically targetable and have accounted for the bulk of recent new product development. Most targeted therapies recognize a protein, rather than the coding gene responsible for that protein. DNA repair mechanisms, however, are closer to becoming reality, and gene therapy is actively being investigated in this regard, with some products already approved. Nonetheless, the vast majority of precision medicine products targets proteins.

PMG Model Increases the Probability of Success

In its analysis of hundreds of clinical trials, Precision Medicine Group has demonstrated knowledge that can be applied to increase the chances of product success – knowledge that needs to be persistently and pervasively applied early in product concept development. Different from past processes, the therapeutic indication(s) can be determined, the population defined, and the efficient design of bench, animal, and human testing accurately planned well before the first animal or human is exposed to an experimental product.

We have termed such product-targeted design Precision Medicine Knowledge Frame # 1 (PMKF #1) and it is based in target identification and then biochemical and biophysical scientific product design and experimentation. PMKF #1 is the first critical application of up-to-date scientific and medical data. This, first step of product concept and design is required but often is not sufficient to have a specific physiologically measurable effect. It shows the way to further development.

The new business model implicates the Precision Medicine Knowledge Frame #2 (PMKF #2) or the deep scientific and medical investigation of the interactions such a drug or biologic will encounter once inside the patient with the target disease.[11] These changes in DNA, RNA, protein functions, concentrations and physiologic impact, local and systemic physiology, immunology and often local and systemic environmental abnormalities have been demonstrated to have a dramatic impact on the success or failure of a well-designed targeted product in human diseases. The lack of Precision Medicine Knowledge Frame #2, particularly regarding the nature of diseases in human populations, has led to a large proportion of experimental product failures.

Analyses demonstrate that the PMKF #1 conceived and developed experimental product usually performs exactly as biochemically designed. However, precision biochemical and biophysical knowledge within the "diseased" human environment (PMKF #2) has often not been sufficiently appreciated by some product development companies and led directly to product failure.

The continual acquisition of scientific and medical knowledge has aided the evolution of precision medicine to recognize the role of many proteins, normal or abnormal in structure, and their respective normal versus abnormal concentrations, functions, and impacts on disease in humans. These local and systemic "proteomic" variations and precise pharmacologic modulations are therapeutically important in cancer, rheumatology, immunology, and other therapeutic areas; hence, proteins (e.g., receptors, cytokines, enzymes) involved in the respective disease processes are targeted.[13-15]

Less than 2% (on the order of 25,000 genes) of the human genome actually codes for proteins,[13,14] whereas 98% is "noncoding," and a large percentage (~80%-90%) of those sequences are actually translated into a defined group of noncoding RNA species (ncRNA, a form of non-messenger RNAs).[16,17] Of significant note, ncRNAs play a substantial role in controlling protein production, cellular-wide regulation, RNA-enzyme activity, and many structure abilities that regulate homeostasis and disease states. DNA damage can similarly occur in protein coding and noncoding regions of the human genome, and these ncRNAs are now known to be critical in the biochemistry and biophysics of normal and abnormal cellular function.[18] These ncRNAs have been demonstrated to play a major role in many disease states where mechanism has not previously been elucidated. Capturing this and newer knowledge during the product development process is key to improving the historically low rates of new products achieving market approval.

"The lack of up-to-date scientific and medical knowledge regarding the human population treated, has led to a large proportion of experimental product failures."

Changing Pharmaceutical, Biologic, and Device Success Rates

Though FDA drug approvals have approximately doubled on average year over year since 2004 (from 20 to 30 per year to 40 to 50 per year), the introduction of new drugs and biologics to first-in-human clinical trials has increased even more dramatically. In a recent MIT analysis of 406,038 clinical trials studying 21,143 compounds, a probability of success (market approval) for all products analyzed was 13.8%.[19] Viewed another way, approximately 86.2% of new clinical products *fail* to attain approval. Additionally, the FDA approval rates are much higher in non–precision medicine therapeutic areas. Oncology, perhaps the highest intensity precision medicine therapeutic area, has the lowest probability of success for new compounds entering human clinical trials, just 3.4%. Vaccines, ophthalmology, infectious disease and endocrinology/metabolism have the highest probability of success among products entering human clinical trials: 33.4%, 32.6%, 25.2%, 19.6%, respectively.[19]

The reasons for the low success rates in all therapeutic areas are endlessly debated. For example, despite having well-defined, decades-old pathways for non–precision drug development, product approval in all classes of non–precision medicine areas still suffer failure rates of about 50% to 80% in human clinical testing. New technologies/product classes can also be handicapped because of novel toxicities and methods for measuring safety and efficacy. Dire complex diseases such as cancer (often heterogeneous by nature) have proven more difficult than anticipated to be treated successfully, perhaps explaining some of the high failure rates.

The bench science of precision medicine uses present-day knowledge to identify targets and strategically develop very specific therapeutics to perform the designed biochemical task. If this low success rate is a result of a lack of efficacy or a safety profile that is not manageable within the normal flow of patient care, these products will not reach widespread distribution. However, what if these products are shelved (see case study) because of a lack of known critical knowledge that impacts success or failure?

The goal at Precision Medicine Group has been to assist researchers and companies to attain these critical new knowledge sets, understand the impact on their product development plan, and increase the likelihood of success. In the past decade, this avalanche of critical knowledge has punctuated the need for new business structures, product development processes, regulatory science, and commercialization programs that are congruent with the new precision scientific and medical paradigms.

Precision Business Model Based on Constant Learning and Integration

As a result of these changes, recent therapy entrants to market present stiff competition due to shorter product development timelines and greater efficiency in generating data faster and at lower cost. In light of this, the Precision Medicine Group was designed to identify, tackle, and reform pharmaceutical, biologic, and device development processes using known data and efficient application to move new products to marketing approval at a higher rate. With its mission to meet the scientific, medical, and commercial needs for innovative new products, Precision Medicine Group offers a blueprint for the future. As shown in **Figure 2**, the approach has two components.

Case Study of STING Agonist Development[12]

Multiple biotechnology and large pharmaceutical companies have collaborated on the development of "STimulator of INterferon Genes", or STING, therapeutics that induce DNA transcription (through 8 or more biochemical steps) to form Interferon mRNA Interferon protein translation and secretion into the environment. Biochemically and Biophysically designed STING binding products have been demonstrated to specifically and sensitively activate (as agonists) the normal cytoplasmic molecule. Animal model studies were extremely encouraging. Many clinical trials using this hypothesis began in human subjects.

The goal was to increase Interferon production and stimulate the immune system to kill tumor cells. In analyzing these studies carefully, Precision noted that the Precision Knowledge Frame #1 was in large part scientifically fulfilled. The drug as designed definitely bound STING and activated its initial pathway reaction. The PMKF 1 analysis demonstrates the STING pathway has many subsequent biochemical steps leading from this initial cytoplasmic STING activation to DNA transcription, translation and interferon secretion. Subsequently, Precision Medicine Knowledge Frame 2 was then examined regarding the systemic and local interaction of interferon with appropriate immune cells. Precision Medicine identified several issues, but one important, as-yet unrecognized item appeared in the analysis of these trials: the absolute requirement for immune cells to be functionally active inside the tumor microenvironment and to have a measurable response. All comers were entered into these studies regardless of the baseline tumor immune microenvironment categorization. Some responses were noted, but few. These sparse responses corresponded to predicted proportion of very "warm" to "hot" tumors (i.e., significant immune activation present within the tumor) for the histological types enrolled. Though efficacy had been very high in the animal models, it was concluded by many that efficacy in humans was much lower and many of these programs have been placed on a shelf. Precision hypothesized that by simply measuring the "immune hotness" of the tumors at baseline and then selecting subjects with only very warm to hot tumors, the therapy would have demonstrated a higher potential for treatment efficacy in that responder population and development would have continued.

Research and Development

One essential component is connecting comprehensive translational science knowledge to the development of precision medicine, including companion diagnostics. Specifically, Precision's bench scientists understand both the physiology and biochemistry associated with targets of today *and* tomorrow. The work performed is designed to gain rapid information and safely and effectively apply this knowledge to human trials. Precision's computational biologists, programmers and big data experts help our scientists and physicians remain not only up-to-date but looking for the data needed by our clients two to three or more years into the future. This foresight is critical to ensure that the right samples are collected during clinical studies, allowing for flexibility in sample testing as technology changes and improves.

Medically, Precision physicians and experts assist product companies in designing preclinical, nonclinical, and human studies that incorporate in-depth understanding of patients with disease, identification of individualized biochemical and biophysical barriers to success, and proven successful development strategies, e.g., specific population testing and selection. Accelerated designs, safety knowledge, and up-to-date pathways to efficacy measurement are well planned prior to the first patient entering a trial.

Summary

The world of medicine, science, and human health product development has been significantly disrupted from past processes. In brief, the Precision Medicine Group believes that product development is much different and more complex than in the recent past and today requires newer thinking, advanced business models, and diverse, profound expertise. Precision Medicine Group was specifically built to bring these capabilities and the consequent substantial increase in relevant new information and up-to-date knowledge to human health product development companies. Ideally, this vast amount of information will be sorted, analyzed, and applied early in the bench science, the therapeutic target concept phase, preclinical safety and efficacy testing and then through human testing design, performance and success.

Precision has discovered many times that important data exists that could have avoided failures in drug development and increased the ability to gain approval efficiently. Well-designed, large database evaluations of human disease have been used to identify product-specific and required science knowledge (often seemingly unrelated, disparate, or obfuscated) that allows experts from both a client company and Precision to plan the full developmental pathway early.

The Precision Medicine Group model recognizes the daily increase of pertinent knowledge of human-altered physiology in sickness that can efficiently advance the development of innovative new treatments. We leverage the convergence of development and commercialization methodologies in this model to increase the likelihood of regulatory approval and generate greater market access for new products. JoPM

Precision Medicine Group

Founded in 2012 by Ethan Leder (son of "precision" medicine pioneer Phil Leder) and Mark Clein, Precision Medicine Group is an organization with a scientific pedigree and built for "precision" in science and medicine. According to the company, "With the discipline of precision medicine as our foundation, Precision Medicine Group has brought together targeted expertise in fields from advanced lab sciences to transformational informatics and regulatory affairs, payer insights to marketing communications. We apply relevant insights and specialized capabilities to unlock the potential of data – accelerating drug development, advancing manufacturing, and elevating engagement to deliver commercial success."

"Precision Medicine Group website section The Story, Story | Precision Medicine Group (precisionmedicinegrp.com)"

Precision Medicine Group website initial page, Precision Medicine Group (precisionmedicinegrp.com)

Deborah Phippard, PhD

Deborah is the Global Head of Research at Precision Medicine Group, Precision for Medicine. She has 25+ years of Immunology basic science research, assay development and understanding. She oversees the Precision for Medicine worldwide system of cutting-edge specialty labs. This embraces vast access to specimens, validated academic, new and common bench processes to support the early innovative often first-in-class new product concepts. Her expertise is in precision science for new products, new targets and pathways, and diagnostics for population selection to efficiently move to human trials and marketing approval.

Gerald L. Messerschmidt, MD, FACP

Gerald is the Chief Medical Officer at Precision Medicine Group, Precision for Medicine. He has 40 years of medical expertise, still teaches physicians, and has been involved with hundreds of products developed and approved. He reads science and medical articles and new findings constantly. His expertise is in precision medical issues and how these impact product development, failure, and success in obtaining marketing approval worldwide.

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Footnote

* To avoid ambiguity of terms, the Journal distinguishes between precision and personalized medicine. Precision medicine is the design, development, and validation of a biomarker or drug (small molecule, biologic, or vaccine) based on population statistics intending to treat a category of patients who would best benefit from a diagnostic or therapeutic. Personalized medicine is the practice of treating patients with a precision medicine based on, e.g., the patients' clinical data (gene profile, biomarkers, clinical data), family history, patient history, lifestyle, and current drug prescriptions.