whom clopidogrel is the best and least expensive antiplatelet agent available.

We have known since time immemorial that every drug produces variable effects across populations, and we now understand the genetic basis for some of that variability. So why is *CYP2C19* testing not the standard of care to guide antiplatelet therapy? The logistics of widely implementing pre-prescription genotyping are nontrivial. Whether point-of-care testing with a rapid turnaround time (as in some of the patients in the POPular Genetics trial) or preemptive testing (placing important pharmacogenetic results in electronic records with decision support that is triggered when a target drug is prescribed)[9] is most effective remains to be defined. Costs remain a moving target, and earlier simulations that estimated the cost of incorporating genotype data[10] into prescribing should now be reexamined.

The POPular Genetics trial provides strong support for a genotype-guided approach to clopidogrel prescribing in patients of European ancestry, in whom the contribution of *CYP2C19* variants was first defined; a minority of patients of European ancestry carry loss-of-function variants, and very few are poor metabolizers. The result has even greater implications for parts of the world where these variants are much more common. Professional societies, which increasingly view atherosclerosis as a worldwide epidemic, must now rethink their stance with respect to genotyping to improve the effectiveness of clopidogrel therapy.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Drug Regulation in the Era of Individualized Therapies

Janet Woodcock, M.D., and Peter Marks, M.D., Ph.D.

Kim et al., in a report now published in the *Journal*,[1] describe the discovery, development, and administration of an antisense oligonucleotide (ASO) therapy specifically designed for a single patient with CLN7 neuronal ceroid lipofuscinosis (a form of Batten's disease), a fatal genetic neurodegenerative disorder.[2] In this patient, a known pathogenic point mutation was found to be present in one copy of the gene *MFSD8* (also known as *CLN7*), and a previously undescribed insertion of a retrotransposon was present in the other copy. Retrotransposons are stretches of DNA that are sometimes described as mobile elements; thousands are present in the human genome, and some are capable of moving to a new location — such as the middle of a gene — through a "copy and paste" mechanism. The authors showed that the retrotransposon inser-

tion in this patient led to missplicing of the *MFSD8* messenger RNA (mRNA) and probably to premature translational termination. The authors devised candidate ASOs that were intended to "correct" the missplicing of the mRNA and selected a candidate ASO that, in cultured patient fibroblasts, resulted in an increase in the ratio of normal to mutant mRNA. Evaluation of lysosomal function in vitro showed improvements in the presence of the ASO. After an abbreviated toxicologic evaluation and after obtaining authorization from the Food and Drug Administration (FDA) and expedited institutional review board approval, the investigators administered the compound intrathecally to the patient in ascending doses.

This patient and a few others — including a person with idiopathic multicentric Castleman's disease that was refractory to blockade by interleukin-6, who identified a specific signaling pathway as a target in his own disease — illustrate how recently developed technologies permit the delineation of pathways for truly individualized drug development.[3,4] Academic clinician–investigators now have the capacity to rapidly uncover specific mutations and pinpoint the putative mechanisms leading to certain rare disease phenotypes. Various ASOs or other compounds can be produced by third parties, and investigators can evaluate them using in vitro assays or animal models. Similarly, genetic constructs can be developed for cell-based or directly administered gene therapy. Specialized laboratories can conduct safety testing to support initiation of first-in-human trials, and contract manufacturers can produce a clinical-grade product. Although this new pathway for drug discovery and development is most advanced for ASOs, other types of treatments, including individualized cell and gene therapies, are following closely behind.

In these "N-of-one" situations, what type of evidence is needed before exposing a human to a new drug? Even in rapidly progressing, fatal illnesses, precipitating severe complications or death is not acceptable, so what is the minimum assurance of safety that is needed? How persuasive should the mechanistic or functional data be? How should the dose and regimen be selected? How much characterization of the product should be undertaken? How should the urgency of the patient's situation or the number of people who could ultimately be treated affect the decision-making process?

In addition, how will efficacy be evaluated? At the very least, during the time needed to discover and develop an intervention, quantifiable, objective measures of the patient's disease status should be identified and tracked, since, in an N-of-one experiment, evaluation of disease trends before and after treatment will usually be the primary method of assessing effectiveness. In this regard, there is precedent for the application of new efficacy measures to the study of small numbers of patients.[5]

This new drug-discovery paradigm also raises many ethical and societal issues. Patients and their families, of necessity, function more like project collaborators than traditional trial participants: it is easy to envision situations in which caregivers or the patient believe there has been disease improvement or stabilization that is not apparent to the investigators. Therefore, "stopping criteria" should be discussed, ideally with the assistance of an ethicist, before administration of the treatment, to provide some common understanding of what measures of effectiveness might be used. Thought will need to be given to how to react to the occasional failures of this drug-development paradigm that will inevitably occur and potentially be associated with serious adverse events. Consideration also needs to be given to how to proceed if the intervention appears to be helpful and other patients with the same mutation are subsequently identified. On a larger scale, we need to consider how such truncated programs fit into the spectrum of drug development in general: what are the differences between treating one, ten, or thousands of patients? Although the FDA and other regulators typically allow streamlined preclinical data generation for rare, serious diseases, programs for a single patient are likely to set the floor for the minimum preclinical evaluation. How should this be escalated for slightly more prevalent diseases of equal seriousness?

If such individualized interventions become common, and some are successful, the questions of regulatory approval and sustainability of production also become pertinent. Some investigational products, such as snake antivenins, have remained investigational for decades, maintained by various nonprofit or governmental organiza-

tions. Approvals as variations on a well-characterized archetypal product might be feasible if the interventions are closely related. Finally, finding sustainable funding for such interventions may prove challenging, because the cost of production can be quite substantial, particularly for gene therapies. In the upcoming months, these issues will need to be addressed at the FDA with input from academic, patient advocate, pharmaceutical industry, and other stakeholders.

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