they may have used narrow networks to discourage enrollment by persons with costly conditions.

The potential for provider networks to influence the risk profile of plan enrollees provides an economic rationale for regulation of insurers' networks, but I would argue that CMS and state insurance commissioners should not force insurers to contract with providers or otherwise interfere in plan–provider negotiations. In addition to increasing insurance premiums, network-adequacy regulations risk politicizing insurers' decisions about provider networks — and a provider's success shouldn't depend on its influence with key legislators or regulators. Opponents of the ACA fear that it will lead to reactive, ad hoc micromanaging of the health care system; the "reasonable access" policy does little to assuage this concern. CMS would be wise to limit its role to ensuring that plans make their provider lists readily accessible to consumers before they choose a plan.

Plans could control costs while diminishing consumer concerns about limited choice by making greater use of tiered networks. Tiered networks allow patients to receive care from a broader set of providers but require patients to pay higher out-of-pocket costs if they go outside the core network. If consumers value choice, the market will evolve in this direction without prompting from regulators.

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Genotype–Phenotype Correlation — Promiscuity in the Era of Next-Generation Sequencing

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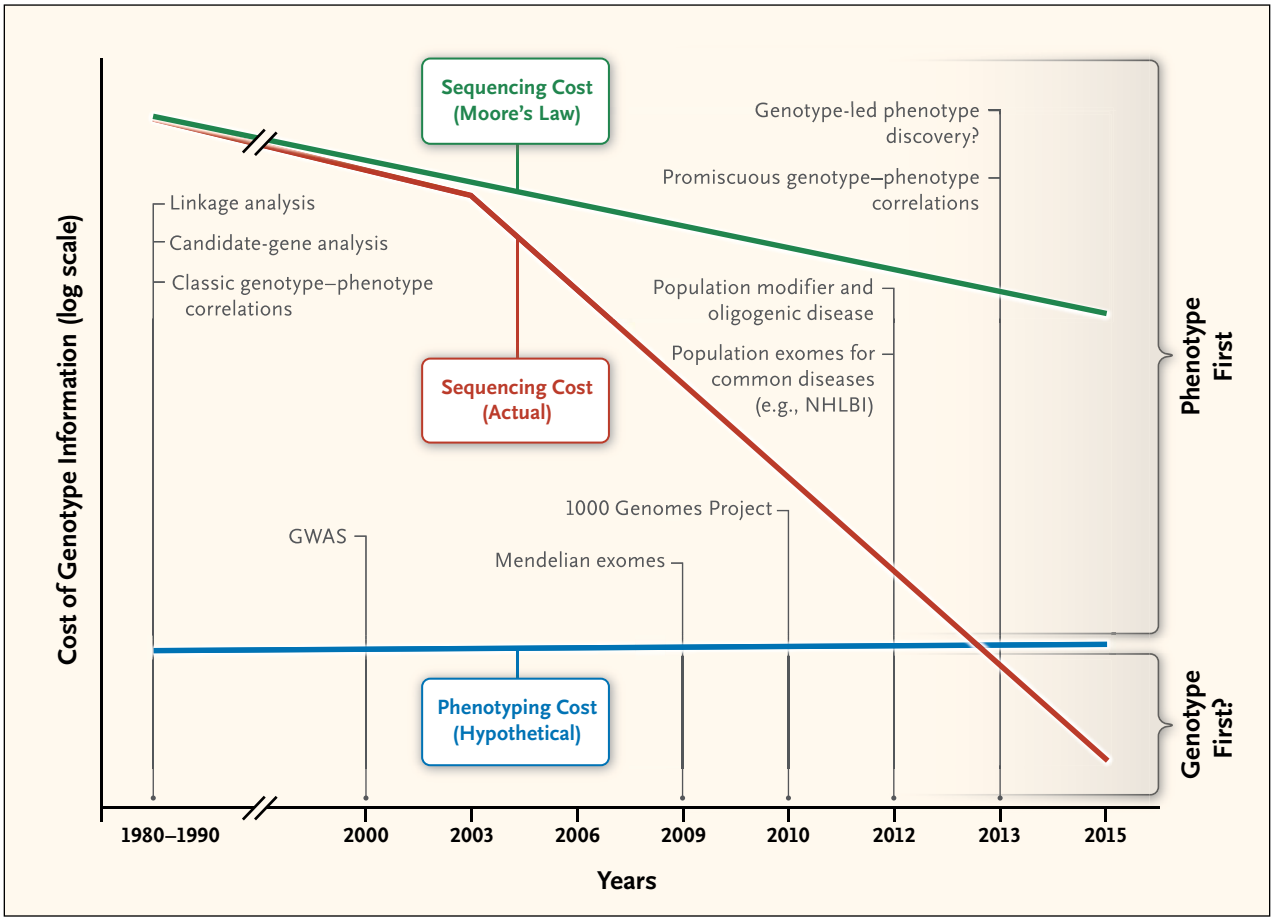
Ever since Mendel observed the varied phenotypes of peas — green or yellow, smooth or wrinkled — phenotypes have been used to systematically identify the genetic causes of disease. Similarly, genotype–phenotype relationships in humans could be dissected only if there were clearly recognizable, and relatively homogeneous, phenotypes. Since broad searches of genetic information were not technically feasible or cost-effective before the advent of next-generation sequencing (NGS), scientists studied well-characterized families to narrow the list of plausible genetic causes. However, being restricted to this set of "solvable" genetic problems led to ascertainment biases that favored highly penetrant mutations with straightforward functional consequences — that is, loss of function, gain of function, or dominant negative mutations dramatically affecting protein function. Thus, genetic studies before NGS systematically underestimated the true amount of genetic variation.

Understanding the extent and sources of this variation is critical in diagnostic applications, since clinical care and treatment options rely heavily on predicting phenotypes from genetic polymorphisms. For many mendelian diseases, single genetic variations (e.g., single-nucleotide polymorphisms, frameshift insertions and deletions, triplet repeats, and copy-number variants) are often good predictors of clinical disease. Yet for most diseases (both common and complex disorders), prediction of clinical and treatment prognoses is challenging because of complex genetic mechanisms and variable expressivity and penetrance.

The advent of cost-effective NGS (see graph) — especially whole-exome sequencing (WES)



The Decreasing Cost of Genotype Information.

Shown is an approximate timeline of milestones in genetics research that have been enabled by the corresponding decline in sequencing costs. Costs are shown as both actual costs and costs if they followed Moore's law (which states that computing power doubles approximately every 2 years). Phenotyping costs are unknown but are assumed to have remained relatively flat as compared with the rapid drop in sequencing costs. Next-generation sequencing has reduced the cost and increased the resolution of genotype–phenotype correlations to the point where knowledge of genotype often drives discovery of phenotypic associations in a previously unexpected fashion. GWAS denotes genomewide association study, and NHLBI National Heart, Lung, and Blood Institute.

— has resulted in an explosion of discoveries of novel genetic mutations that reveal the rampant "promiscuity" of existing collections of genotype–phenotype relationships. In hundreds of studies of mendelian diseases, potentially deleterious alleles that have been discovered through WES have been identified in probands and their relatives. These putatively straightforward cases have produced the expected discovery of high-penetrance, single-locus, rare alleles with functional consequences specific to temporal, spatial, or tissue contexts of developmental and homeostatic pathways.

However, WES has also uncovered a high level of allelic heterogeneity (different mutations in one gene) and locus heterogeneity (mutations in different genes) associated with even simple mendelian diseases. This promiscuity of genotype–phenotype association means that less restricted correlations of altered protein structure are associated with limited disturbances of biologic function. Studies of pediatric diseases such as Kabuki syndrome and Schinzel–Giedion syndrome revealed that allelic combinations of missense, nonsense, and compound heterozygous mutations within different genes could have similar functional effects that lead to overlapping clinical phenotypes. In contrast, allelic heterogeneity in diseases such as laminopathies

resulted in disparate phenotypic outcomes because of the distinct functional effects of each particular variant in different tissues. For example, different polymorphisms in lamin A and lamin C can cause distinct skeletal, neurologic, or metabolic phenotypes. This finding supports the conclusion that there are differential, tissue-specific consequences of specific classes of mutations in proteins that may otherwise function more broadly during development and homeostasis.

Furthermore, many WES studies also identified large subpopulations of patients with overlapping clinical presentations that did not have deleterious variants in identified disease genes. For example, only 26 of 43 patients with the Kabuki syndrome had mutations in the causative gene, *MLL2*. And in a study of 300 patients with sporadic high myopia, only 5 had mutations in candidate gene *ZNF644*.[1] In addition to indicating locus heterogeneity, these results suggest that complex genetic mechanisms involving oligogenic inheritance, with multiple causative alleles, modifier alleles, or both, are probably more common than previously appreciated.

Phenotypic variation in some diseases has also been demonstrated to reflect diverse inheritance mechanisms. These diseases include retinitis pigmentosa (digenic inheritance involves the genes *ROM1* and *PRPH2*), thrombocytopenia with absent radius syndrome, and facioscapulohumeral muscular dystrophy type 2. In another example, mutations in the gene encoding type I collagen, the most common protein component of bone, were the only known genetic cause of osteogenesis imperfecta for more than 25 years. With the application of NGS, mutations in more than 13 genes — which play roles in collagen processing and transport, bone-cell differentiation, and intercellular and matrix-cell signaling — are now known to affect low bone mass leading to increased fracture risk in patients with osteogenesis imperfecta. Here, secondary causative and modifier alleles seem to conform to the model of clan genomics or mutational burden: they have rare, recent deleterious mutations that, though individually necessary, are not sufficient to cause disease without other mutations.[2]

In addition, oligogenic causation is becoming one of the leading explanatory theories for disease systems such as ciliopathies. Though the theory is still being debated, variability in the clinical presentation of these diseases of primary cilia — 15 clinical syndromes with overlapping combinations of developmental abnormalities (e.g., skeletal anomalies, polydactyly, and intellectual disability) and degenerative phenotypes (retinal degeneration and renal cystic disease) — are hypothesized to be caused by combinations of more than 50 primary loci (with population frequencies of <0.1% for deleterious variants)[3] interacting with modifier and secondary causative alleles. Although the relative rarity of in trans combinations of these variants (one variant from each parent) complicates our ability to validate genotype–phenotype correlations, the scalability of sequencing should reduce the burden over time. The challenge will then lie in determining what combination of statistical proof with high- and low-throughput in vitro and in vivo validations will be required before combinations of rare variants in multiple genes are accepted as pathogenic.

Although the genetic causes of more than 60% of suspected mendelian phenotypes cannot be immediately determined with current NGS analysis methods,[4] continued collection, characterization, and sequencing of mendelian and common complex diseases will provide new opportunities to unravel the developmental and homeostatic mechanisms governing specific tissues. As WES or whole-genome sequencing is expanded into systemically, comprehensively characterized clinical populations, these patients provide a natural experimental condition for correlating genetic variation with phenotypic heterogeneity documented in clinical records. Although quantitative studies of associations between rare and common variants might require the genetic sequencing and phenotyping (and potential repeat phenotyping) of more than 25,000 people,[5] recent discoveries in dyslipidemias, psoriasis, and type 2 diabetes suggest that the identification of rare coding variants in large populations is already establishing a catalogue of mutations of variable penetrance that alter physiological pathways in common disease phenotypes. Detection of these allelic combinations will help researchers identify key pathogenetic pathways and groups of novel therapeutic targets.

The vast quantity of data provided by research and clinical sequencing is daunting, yet their strategic use can improve clinical outcomes. We anticipate that usage patterns for genomic data will largely depend on their predictive power. In cases of highly

penetrant genetic mutations that predictably result in disease, clinical sequencing will enable individual screening, monitoring, prevention, and treatment of medically actionable conditions. On the other hand, there will be a large proportion of potentially deleterious variants associated with medium-sized odds ratios for disease and variable phenotypic predictive power. In keeping with evidence-based clinical decision making, such biomarkers should be used in conjunction with clinical observation, laboratory tests, and empirical treatment to refine estimates of the probability of disease and treatment prognoses. For example, knowledge about *CYP2C9* mutations in cytochrome P-450 should lead to the development of decision-support tools that influence the administration of warfarin and other drugs that use the same metabolic pathways.

Ultimately, clinical use of sequencing data should reduce the cost of care. If genetic information can be stored, analyzed, and disseminated in a private, cost-effective, and timely manner, precise and affordable molecular and genetic diagnoses should result in more specific treatment guidelines and avoidance of costly diagnostic and therapeutic procedures. Furthermore, supplementing clinical intuition with molecular diagnoses in syndromes with overlapping symptoms may reduce variance in diagnosis and treatment outcomes between academic medical centers and community hospitals and clinics. Although additional molecular and informatics research is needed, we are confident that NGS will eventually revolutionize clinical care just as it is revolutionizing the scientific endeavor.

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When Religious Freedom Clashes with Access to Care

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At the tail end of this year's Supreme Court term, religious freedom came into sharp conflict with the government's interest in providing affordable access to health care. In a consolidated opinion in *Burwell v. Hobby Lobby Stores* and *Conestoga Wood Specialties Corp. v. Burwell* (collectively known as *Hobby Lobby*) delivered on June 30, the Court sided with religious freedom, highlighting the limitations of our employment-based health insurance system.

Hobby Lobby centered on the contraceptives-coverage mandate, which derived from the Affordable Care Act (ACA) mandate that many employers offer insurance coverage of certain "essential" health benefits, including coverage of "preventive" services without patient copayments or deductibles. The ACA authorized the Department of Health and Human Services (HHS) to define the scope of those preventive services, a task it delegated to the Institute of Medicine, whose list included all 20 contraceptive agents approved by the Food and Drug Administration. HHS articulated various justifications for the resulting mandate, including the fact that many Americans have difficulty affording contraceptives despite their widespread use and the goal of avoiding a disproportionate financial burden on women. Under the regulation, churches are exempt from covering contraception for their employees, and nonprofit religious organizations may apply for an