become mandatory, as it ultimately did with children. Congress also may strengthen earlier mandates, as in the case of aged, blind, and disabled beneficiaries. Not infrequently, as the "floor" is raised, states are offered new options to again move beyond that floor. This has been Medicaid's pattern since 1965, and states know that.

Coverage of poor, nonelderly adults has similarly followed this pattern. Under current law, states must cover certain categories of nonelderly adults: adults who are pregnant or would have qualified for AFDC before it was abolished and, with certain exceptions, nonelderly SSI recipients. But states have long had the option of offering more generous coverage for pregnant women, nonelderly adults with disabilities, and parents. Indeed, the ACA gave the states the additional option of immediately covering all nonelderly low-income adults — something that several states have already done.

On January 1, 2014, coverage of all nonelderly adults with family incomes below 133% of the poverty level will become mandatory, with the federal government initially absorbing 100% of the cost (and eventually 90%) instead of the far lower financial contribution rates used for other mandatory eligibility groups. In expanding Medicaid, Congress built on what was already in place instead of reinventing the wheel. By covering poor adults in addition to poor children, Congress will finally have established as national policy the floor of coverage for low-income Americans that began to be built in 1965.

From a legal perspective, nothing about this latest Medicaid expansion is different from past expansions, other than the fact that it passed as part of a broader health care reform effort. This fact does not change Medicaid's fundamental status as a voluntary program. Were a state to decide that it would rather end its Medicaid program than cover poor adults, it might have to devise a health care alternative for its poorest residents. But that has always been the question states face when Congress expands Medicaid. States may be confronted with a "hard choice," in the words of the 11th Circuit, as to whether to continue participating in Medicaid. But that is not a constitutional matter.

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1. Florida et al. v United States Department of Health and Human Services, Petition for Writ of Certiorari (Sept. 27, 2011), pp. 16-26.
2. South Dakota v Dole, 483 U.S. 203 (1987).
3. Florida et al. v United States Department of Health and Human Services, 648 F 3d 1235 (Eleventh Cir., 2011), pp. 1265-6.
4. Cohen IG, Blumstein JF. The constitutionality of the ACA's Medicaid-expansion mandate. N Engl J Med 2011. DOI: 10.1056/NEJMp1113416.
5. 42 U.S.C. §1304.

Preparing for Precision Medicine

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Ms. H. is a 35-year-old woman from Japan who has had a cough for 3 weeks. Her physician sends her for an x-ray and CT scan that reveal an advanced lesion, which a biopsy confirms to be non–small-cell lung cancer. She has never smoked. Can anything be done for her?

Had Ms. H.'s cancer been diagnosed before 2004, her oncologist might have offered her a treatment to which about 10% of patients have a response, with the remainder gaining a negligible survival benefit and experiencing clinically significant side effects. But her diagnosis was made in 2011, when her biopsy tissue could be analyzed for a panel of genetic variants that can reliably predict whether the disease will respond to treatment. Her tumor was shown to be responsive to a specific targeted agent, whose administration led to a remission lasting almost a year; her only side effect was a rash.

This scenario illustrates the fundamental idea behind personalized medicine: coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements — hence the term "precision medicine." Recent biotechnological advances have led to an explosion of disease-relevant molecular information, with the potential for greatly advancing patient care. However, progress brings new challenges, and the success of precision medicine will depend on establishing frameworks for regulating, compiling, and interpreting the influx of information that can keep pace with rapid scientific developments. In addition, we must make health care stakeholders aware that precision medicine is no longer just a blip on the horizon — and ensure that it lives up to its promise.

Health Care Stakeholders and Their Roles in Ensuring the Success of Precision Medicine.

Stakeholder	Recommended Actions
Government	Generation of transparent privacy laws Identification of socioeconomic priority areas likely to benefit most from precision-medicine strategies Public consultation regarding "opt in–opt out" strategies for research participation
Research industry	Development of effective clinical decision support tools for integration into electronic health records Setting up and conducting appropriate pilot studies for data collection in targeted precision-medicine areas
Biomedical community	Changes to undergraduate training to develop improved understanding of molecular mechanisms involved in disease Development and contribution to an evolving new system of disease classification incorporating emerging molecular information Introduction of a more transparent, participatory role for patients considered for recruitment to clinical trials
Pharmaceutical industry	Development of effective diagnostic tests with or without tandem therapeutic agents for management of conditions identified as major socioeconomic burdens
Patient groups	Increasing participation in health and well-being initiatives Use of novel means of providing data for research purposes, including social networks and mobile phone applications
Regulatory bodies	Ensuring that regulatory frameworks are in place to safeguard patient safety, while ensuring that scientific progress is not hampered

First, consider regulation: precision medicine is expected to herald a rapid acceleration in the identification and development of next-generation pharmacotherapies. Currently, medical research organizations are calling for regulatory bodies to review the regulation of clinical trials, citing excessively lengthy approval processes as an impediment to the effective translation of basic science discoveries. According to Cancer Research U.K., there was a 65% increase in the time taken to gain approval for studies and a 75% increase in administrative costs between 2003 and 2007.[1] Moreover, there's no evidence to suggest that additional bureaucratic stringency has led to improved patient safety. It will be critical to the success of precision medicine to implement more streamlined approval processes, possibly including more proportionate approaches to regulatory requirements for clinical trials, with consideration of previous experience with a given agent or study population. In addition, precision medicine will mean a departure from traditional clinical trial frameworks, with phase 3 trials focusing on a more select patient group; this narrowed focus should facilitate procedural streamlining and enhance clinical and economic effectiveness.

The U.K. government recently announced new measures aimed at reducing the time from drug development to clinical application, a move that's likely to stimulate similar proposals elsewhere. Ultimately, we must get the balance right: regulatory frameworks must be robust enough to safeguard patients' interests and well-being, while not stifling progress in critical early phases of the precision-medicine endeavor.

The shift toward a deeper understanding of disease based on molecular biology will also inevitably necessitate reclassification of disease states incorporating this knowledge. To that end, the World Health Organization's century-old International Classification of Diseases must be modernized to take into account the expanding molecular data on health and disease. A U.S. National Academies working group recently evaluated the potential for developing a "New Taxonomy of Disease" as part of the precision-medicine movement and made recommendations expected to play out over decades.[2] The committee highlighted the need for a revised classification based on intrinsic biology as well as traditional signs and symptoms. It also emphasized the importance of creating an openly available data source that can dynamically incorporate emerging knowledge.

Precision medicine will require handling of multi-parametric data and some proficiency in interpreting "-omics" data, placing new demands on medical professionals, who may be ill equipped to deal with the anticipated complexity and volume of new information. Addressing these challenges will require effective clinical decision support tools and new educational models.

Currently, genetic testing is available for approximately 2000 clinical conditions, and the number of available diagnostic tests is increasing exponentially. The United States and other countries are investing in multibillion-dollar projects to implement effective electronic health records (EHRs). These systems will store comprehensive, individual-specific data

that will be essential as we move toward precision medicine. However, in a U.S.-based survey, physicians reported that EHRs had poor systems for online test ordering and provided only limited decision support in terms of indications for genetic testing, interpretation of test results, and potential impact of results on patients and their families.[3] Decision support tools have the potential to address these limitations and enable precision-medicine approaches to health care by providing clinicians and patients with individualized information and preferences, intelligently filtered at the point of care. They will provide clinicians with options for test ordering; indicate the sensitivity, specificity, and positive predictive value of tests; and aid clinical workflow by providing algorithms to facilitate decisions on the basis of test results.

New training paradigms will also be necessary for tomorrow's doctors, who will benefit from a deeper, more holistic view of illness integrating traditional pathophysiology-based models with emerging molecular mechanisms. This shift would benefit from international-level attention.

Like physicians, consumers are faced with uncertainty; patient–clinician dynamics are changing, and the successful implementation of precision medicine will hinge on patients' adaptation to key changes. Detailed, open-access molecular information raises ethical questions regarding data handling and privacy, and strict regulation will be required. The U.K. government recently announced proposals to consult the public on how patient data could be used more openly in biomedical research, including the use of a new secure Clinical Practice Research Datalink. These measures will help the cause of precision medicine, though successful public engagement will require a cultural shift, with patients viewed not as study subjects but as central participants in the precision-medicine community, able to shape, develop, and disseminate research, given the right opportunities and access.

In addition, the public will need proof that precision medicine can live up to the hype. There have been both notable successes and well-publicized failures. For example, the detection of certain polymorphisms among *CYP450* genes has been suggested as a means of determining the type and dose of selective serotonin-reuptake inhibitors for treating depression. The U.S. Centers for Disease Control and Prevention believes there's no evidence linking *CYP450* testing to clinical outcomes, but that hasn't stopped businesses from offering *CYP450* testing services.[4] Openly expressed scorn regarding such direct-to-consumer diagnostic tests with limited or no clinical utility does little to get the public interested in precision medicine, and such rogue activity is harmful to the cause. We must be pragmatic: precision and clever science will not always lead to clinical effectiveness, but we must implement safeguards against the marketing and distribution of bogus products.

Ultimately, precision medicine should ensure that patients get the right treatment at the right dose at the right time, with minimum ill consequences and maximum efficacy. But it will change how medicine is practiced and taught and how health care is delivered and financed. It will change the way research and development are financed and regulated. It will deeply affect public trust and the nature of the patient–clinician relationship, and it will require unprecedented collaboration among health care stakeholders.

Undoubtedly, significant challenges lie ahead, though none are insurmountable. Yet expectations must be realistic: precision medicine will happen neither automatically nor overnight. The transition should be steered by international consortia including leaders from academia, health care, government, and industry that draw up proposals for public consultation. The World Economic Forum Health Council is currently establishing structured dialogue on the key issues outlined here and suggests that multi-stakeholder adaptation, as outlined in the table, will be critical to the precision-medicine enterprise.

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1. Mayor S. EU must reform clinical trials regulation, warn medical research bodies. BMJ 2011;343:d6215.

2. Committee on a Framework for Developing a New Taxonomy of Disease. Towards precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: National Academies Press, 2011.

3. Scheuner MT, de Vries H, Kim B, Meili RC, Olmstead SH, Teleki S. Are electronic health records ready for genomic medicine? Genet Med 2009;11:510-7.

4. Katsanis SH, Javitt G, Hudson K. A case study of personalized medicine. Science 2008;320:53-4. [Erratum, Science 2008;320:316.]