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A Population Perspective on How Personalized Medicine Can Improve Health

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Abstract

The term P4 medicine is used to denote an evolving field of medicine that uses systems biology approaches and information technologies to enhance wellness rather than just treat disease. Its four components include predictive, preventive, personalized, and participatory medicine. In the current paper, it is argued that in order to fulfill the promise of P4 medicine, a “fifth P” must be integrated--the population perspective--into each of the other four components. A population perspective integrates predictive medicine into the ecologic model of health; applies principles of population screening to preventive medicine; uses evidence-based practice to personalize medicine; and grounds participatory medicine on the three core functions of public health: assessment, policy development, and assurance. Population sciences--including epidemiology; behavioral, social, and communication sciences; and health economics, implementation science, and outcomes research--are needed to show the value of P4 medicine. Balanced strategies that implement both population- and individual-level interventions can best maximize health benefits, minimize harms, and avoid unnecessary healthcare costs.

Introduction

The term P4 medicine was coined by Leroy Hood--founder of the Institute for Systems Biology in Seattle and a pioneer in systems approaches to biology and medicine--to denote an emerging model of medicine that focuses on maximizing wellness for each individual, rather than merely treating disease.[1-3] Dr. Hood’s research focuses on the study of molecular immunology, biotechnology and genomics. His ideas have influenced the modern development of “personalized medicine” at NIH and beyond.[4]

Briefly, P4 medicine describes a systems approach that includes predictive, personalized, preventive, and participatory aspects. This approach extends beyond genomic medicine because “genes and their products almost never act alone, but in networks with other genes and proteins and in context of the environment”. [5] P4 medicine proposes to integrate numerous biologic data points--including longitudinal molecular, cellular and phenotypic

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measurements, as well as individual genome sequences--to better define health or wellness for each person, to predict disease transitions, and to target medical interventions.[3] The premise is that P4 medicine will lead to powerful new diagnostics and therapeutics for treatment and prevention, based on each person's unique biologic characteristics (e.g., inherited variation to drug response) and disease processes (e.g., tumor genomic characteristics). [3]

The potential for the emerging knowledge of genomics to improve health has been anticipated,[6] but actual clinical applications have been limited. [7,8] The emergence of fast, reliable, and more-affordable whole genome sequencing (WGS) is opening the door to higher-resolution analysis of individual genomes and a more thorough exploration of less-frequent genetic variants in both common and rare disorders. [9,10] Whole genome analysis has already produced some successes, such as identifying the cause of an atypical case of inflammatory bowel disease and uncovering a path for effective treatment. [11] Whole genome analysis was recently used to study families with severe arterial calcifications; elucidating the molecular defect in this condition could help in developing interventions. [12]

In addition to whole genome analysis, bench-to-bedside research is already producing numerous tests based on complex biomarkers for use in disease diagnosis, prognosis, and prediction of response to therapy. For example, a database developed by CDC to monitor tests in transition from research to practice has captured more than 300 new tests since 2010. [13] One of the principal tenets of P4 medicine is that stratifying common complex diseases, such as breast cancer, into subtypes based on biomarkers can lead to the development of targeted therapeutics. The use of trastuzumab in *HER2*-positive breast cancer patients is an example of the effectiveness of this approach,[14] although many questions remain regarding implementation, cost effectiveness, and outcomes. [15]

As the clinical application of 21st-century biomedical research, P4 medicine relies more than ever on detailed knowledge of biologic processes. A systems approach to improving health and preventing disease will entail interpreting biologic data related to both etiologies and interventions in a larger context. Systems biology now provides unprecedented opportunities to study and measure the effects of environmental exposures;[16] at the same time, many approaches to wellness and prevention occur outside the context of clinical practice. [17]

The potential of P4 medicine can best be realized through a renewed partnership between medicine and public health. [18-20] In the current paper, the concept of P5 medicine is introduced as a true integration of a population perspective into all four components of P4 medicine (Table 1). Inherent to P5 medicine is the balance between individual and population interventions for improving health and the evaluation of their comparative effectiveness. [21,22] Discussion is presented on how the principles of population sciences and public health practice influence each of the components of predictive, preventive, personalized, and participatory medicine.

Predictive Health Should Be Integrated Into the Ecologic Model

> "Our vision is that, in the not too distant future, each patient will be surrounded by a 'virtual cloud' of billions of data points that will uniquely define their past medical history and current health status. Furthermore, it will be possible to mine the billions of data points from hundreds of millions of individuals to generate algorithms to help predict the future clinical needs for each patient." (Hood and Friend[3])

The concepts of systems biology can be easily incorporated into the ecologic model, in which health is the product of a person's underlying biology and his or her environment, as shaped by family and community and including social, cultural, economic, physical, and policy factors. [23] A model that integrates determinants of health at multiple levels and across the life span can improve our ability to predict the occurrence of disease and to devise better interventions; these include more than new diagnostic markers and targeted drugs and may include new environmental, educational and policy interventions. Traditional epidemiologic thinking about determinants of health and disease is also evolving away from a focus on single causes or "risk factors." "Systems epidemiology" integrates factors operating at multiple levels, including inter-relationships among these factors and dynamic feedback over time.

Galeo et al. recently illustrated this concept, using obesity as an example. [24] Predictive factors included endogenous factors, such as genes and gene expression; individual factors, such as dietary intake, exercise habits, TV-viewing patterns, and income; neighborhood factors, such as availability of grocery stores, walking environment, and food advertising; school-related factors, such as availability of sugary beverages and school health education; industry factors, such as portion-size norms in restaurants and packaged foods; state policies and regulation of food marketing; national food distribution programs and support for various agricultural products; and life-course factors, such as history of breastfeeding, maternal health, and parental obesity. [24]

Ultimately, assessing micro- and macro-level factors as determinants of health and disease requires complex population-based, longitudinal epidemiologic studies. To analyze many variables and their interactions, large sample sizes will be needed, either from single studies or, more realistically, prospectively standardized or harmonized data from consortia, networks, and biobanks. [25-27] Such studies will be costly, involving long periods of follow-up. In addition, new intensive methods for statistical analysis and modeling of multilevel data will have to be developed and validated, in order to distinguish true causal signals from noise (type 1 errors). [28] The same requirements hold for biomarkers and other micro-level indicators "discovered" within millions of systems analyses.

Preventive Medicine Should Abide by Principles of Population Screening

> "The primary challenge will be to mine and integrate these data in the context of the dynamics of biological networks and molecular machines and to construct models of wellness and disease that are both predictive and actionable—and therefore useful to patients and clinicians. Preventive medicine can become a reality as the details of disease perturbed molecular networks open the possibility of using drugs targeted at key nodal points to deter or stop disease progression" (Hood and Friend[3])

In public health, as in medicine, prevention is based on information that is both predictive and actionable, either before disease occurs or in its early stages. Population screening can reduce future morbidity and mortality when it identifies an actionable disease or pre-diseased state in asymptomatic people. A recent issue of "Epidemiologic Reviews" [29] highlighted the evolving scientific foundation for population screening. In an accompanying editorial titled "Screening under scrutiny," Robert Fletcher[30] notes the intellectual advances and the real-world challenges of developing evidence-based screening policies that balance benefits and harms to individuals and populations. Also, Harris[31] states: "with a few exceptions the contribution of screening to improving the health of the public is small, yet it has become a popular and growing form of prevention. It may be that we are learning that the magnitude of benefit from screening is less than we hoped, and the harms may be greater

than we thought". The challenges of applying evidence-based screening principles will increase dramatically as many new biomarkers emerge from P4 medicine.

The ongoing debate about screening for prostate cancer using the prostate-specific antigen (PSA) vividly illustrates the challenge of balancing benefits and harms from screening and subsequent interventions.[32] After years of widespread PSA testing in practice and expensive RCCTs both in the U.S. and in Europe, the U.S. Preventive Services Task Force (USPSTF), an independent multidisciplinary panel that evaluates the evidence around clinical preventive services, recently made a dramatic recommendation against routine PSA-based screening for prostate cancer. [33] The recommendation applies to men in the U.S. population who "do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history".

Although PSA-based screening detects many cases of asymptomatic prostate cancer, convincing evidence suggests that most asymptomatic cancers detected by PSA screening will not progress or are so slow-growing that they will not affect lifespan or cause adverse health effects. Nevertheless, almost all men with PSA-detected prostate cancer currently undergo early treatment with surgery, radiation, or other therapy. Treatment often leads to serious complications, including urinary incontinence, erectile dysfunction, bowel dysfunction, and even (though rarely) death. [33] In addition, from a population perspective, there is the societal investment in unnecessary screenings, diagnoses, and treatments, and expenditure of resources that could be used more wisely.

In P4 medicine, biomarkers emerging from systems biology will need to be evaluated for their potential benefits and harms at both the individual and population levels. For example, multiple single-nucleotide-polymorphism (SNP) profiles that have been associated with increased risk for prostate cancer[34] are available commercially in personal genomic tests sold directly to consumers, without full clinical validation or formal assessments of benefits and harms, or the involvement of healthcare providers. [35] Their evaluation for clinical validity and clinical utility should be as rigorous as that of traditional biomarkers.

The experience with PSA illustrates the difficulty of discouraging the use of a biomarker that has been widely adopted on the basis of incomplete evidence. The cloud of biomarker data following an individual in transition from health to disease has a "natural history" and may contain many "predictors of poor health" that must be understood before it can be considered actionable. [36] Increasing the number of data points will multiply the instances in which decisions will need to be made on whether an individual has passed from being "well" to having a "disease" that requires action. This creates pressure for clinical intervention along this continuum with the potential for both harms and benefits. Given the countless numbers of data points and tests that are to come, tests should be prioritized for validation based on principles of population screening, such as disease burden and the effectiveness and acceptability of interventions. [37]

Evidence-based, population-level approaches to primary and secondary prevention can complement clinical preventive services. Fielding and Teutsch recently described the ways that individual- and population-level approaches can be used to improve health and health care. [38] For example, evidence-based interventions to reduce the burden of type 2 diabetes include those that improve overall health (e.g., increasing education and income), as well as those to control overweight and obesity. Interventions related to urban design, school physical education, diminishing screen time, and workplace programs all stimulate physical activity. [38] Menu labeling, changes in food portion sizes and increasing the availability of affordable, fresh produce can stimulate healthy diets. Comparative effectiveness studies can include population-level interventions along with clinically oriented interventions, such as

screening patients with hypertension for diabetes and recommending lifestyle and medication programs.

Personalized Medicine Needs a Strong Evidence Base for Clinical Practice

> "P4 medicine has the potential to catalyze a sharp turnaround in the ever increasing costs of medical care and, in fact, reduce costs to the point where P4 medicine will be exported to the developing world" (Hood and Friend[3]).

An important hypothesis of P4 medicine is that systems-based biomarkers can be used to stratify complex diseases, such as breast cancer and diabetes, into more homogenous subtypes for targeted therapies (e.g., for *HER2*-positive breast cancer) or treatment stratified according to markers of response (e.g., the field of pharmacogenomics[39]). Most drugs in use today have been developed through trials in patients classified into broad, symptoms-based disease groups (e.g., hypertension, diabetes) rather than into more-refined, pathway-specific categories, with the implicit assumption that people within these broad groups will have similar responses to treatments. Thus, clinical trials (especially Phase III trials) generally require hundreds if not thousands of patients to detect sufficient efficacy and monitor for side effects.

Transition from the conventional classification of diseases to stratification using biomarkers will markedly increase the number of distinct "diseases". This trend is already clear in the field of oncology. For example, lymphoma has already been subdivided into many categories on the basis of histologic patterns and molecular markers, such as receptor status or the presence of a genetic mutation. [3] More data will come from whole genome analysis from the U.S. and international collaborations (e.g., the Cancer Genome Atlas, [40] and the International Consortium of Cancer Genomics[41]). This could have a direct impact on the requirements of clinical trials to include a sufficient number of patients in disease subgroups.

The practice of medicine today is already personalized according to characteristics such as age, race, and gender, as well as other clinical factors, and is subject to rules of evidence, especially for coverage and reimbursement. Further personalization based on biologic pathways adds a substantial layer of complexity. Despite claims that P4 medicine will reduce healthcare costs, the results could easily be the opposite. [42-44] The use of new biologic applications with uncertain clinical utility can waste limited healthcare resources if it diverts resources from effective interventions to minimally effective, ineffective or even harmful interventions.

Several efforts over the past few years have attempted to apply principles of evidence-based medicine to emerging genomic applications (e.g., the Evaluation of Genomic Applications in Practice and Prevention Initiative (EGAPP[45]), and this will continue to evolve in the coming years. How to adapt and apply evidentiary standards for novel "personalized" applications is a matter of ongoing debate. However, two crucial concepts in a given clinical scenario remain the same as in other areas of medicine: clinical validity (association between a biomarker and a clinical phenotype) and clinical utility (improved outcomes and balance between risks and benefits). [46]

The lack of information on the clinical utility for most proposed P4 applications produces an evidence dilemma and a conundrum for implementation into practice. [47,48] Ideally, RCCTs should be done and the necessary sample sizes may indeed be smaller, if the trials are based on validated biomarkers. Unfortunately, there is a recent example of a premature clinical trial, using molecularly driven signature tests that had not undergone sufficient clinical validation. [49] Three other molecularly informed trials to predict the impact of chemotherapy

in lung and breast cancer were suspended in 2011 due to nonreproducible evidence on validation of molecular signatures.[50]

Existing processes for generating and evaluating evidence may be slow, costly, or too unrepresentative to provide useful evidence to decision makers. Recently, comparative effectiveness research (CER[51]) has become more prominent as an approach to finding out "what works" in health care. As defined by IOM, CER is "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care[51]."

Concerns about effectiveness of health care have promoted interest in CER, culminating in the recently established Patient Centered Outcomes Research Institute (PCORI[52]). PCORI responds to concerns that patients, providers, families, and caregivers do not have the specific information they need to make choices aligned with their desired health outcomes. Thus, the concept of personalization is embedded in the PCORI. For example, one of the tenets of this research includes answers to these questions "Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?" "What are my options, and what are the benefits and harms of those options?" [53]

These same questions should apply to P4 medicine. [53] Personalizing health care according to patient preferences will require incorporating social and behavioral information from the outset, not just at the end of the process when a new application is ready for clinical use. Given the large amount of emerging information, it remains to be seen how much evidence will have to come from comparative RCCTs, observational studies, natural experiments, adaptive trials, pragmatic trials, evidence synthesis and modeling. [53]

Participatory Medicine Calls for a Strong Role for Public Health Science and Practice

> "The challenges in the implementation of P4 medicine are twofold: technical and societal. Ultimately, we believe that the societal challenges will prove more difficult to overcome". (Hood and Friend[3])

Implementation of P4 medicine requires full participation and education of patients, physicians, and the entire healthcare community. This participatory role has been viewed by Hood and Friend[3] as important in terms of creating the necessary information and information technology to deal with the exponential growth of data on each individual. Nevertheless, the population perspective encompasses much more than unidirectional provider and consumer education about the power of P4 medicine. It also sets the stage for stakeholder engagement, equity, access, coverage, and choice among alternative approaches. In the U.S., where healthcare resources are limited and inequitably distributed (e.g., millions of people have no healthcare coverage), society has a stake in assuring that the national investment in research leads to tangible health benefits for all and does not worsen existing health disparities. [54]

Glasgow and colleagues[54] have recommended that, in addition to the 4 P's of P4 medicine, societal investment in research should focus on the "4 W's": Who pays?; who benefits?; who suffers?; and who profits?. The practice of medicine occurs at multiple levels of intervention including patient-provider dyads, healthcare organizations, families, communities, and state and federal agencies, all appropriately viewed by the IOM as part of the "public health system". [55] With advances in information technology and a strong direct-to-consumer movement, public health will have an increasing role in collecting population-level data; developing policies for both for empowering and protecting consumers; and assuring that the most-vulnerable segments of the population will have access to and

benefits from validated P4 medicine applications. These three core public health functions--assessment, policy development, and assurance--were first described by the IOM in 1988[56] and have been extended to include the applications of genomic medicine. [57-59] The public health functions provide an important basis for maintaining an appropriate balance between the forces of "premature translation" (i.e., use of nonvalidated or potentially harmful genomic information in practice) versus "lost in translation" (i.e., limited access and disparities for validated technology in population subgroups), [60] as well as addressing issues of value, cost and cost effectiveness.

Finally, in order to fulfill the promise of P4 medicine, public health sciences are crucial for evaluating discoveries beyond the traditional bench-to-bedside model. [61] For example, epidemiologic studies based on large population studies are needed to not only accelerate discoveries but also characterize promising applications for their potential for prediction, prevention, and response to treatments. Behavioral, social and communication sciences[62] will answer key questions about biologically modulated responses to behavioral interventions, public acceptance and adherence to interventions, and decision making in health care.

Implementation science, [63] health services and policy research, [64] CER, [65] economic analyses, and regulatory science[66] all have a role in evaluating how validated applications can move into practice and for measuring their effectiveness and cost effectiveness. Knowledge synthesis, evidence reviews, simulation and economic modeling will facilitate policy decisions and evidence-based recommendations. [61] Several independent and multidisciplinary panels have recently made specific recommendations for enhanced public health research and policies for moving basic science innovations into practice. [61]

Conclusion

Although the tenets of P4 medicine—predictive, preventive, personalized and participatory — refer to individual health, success of the P4 enterprise depends on the integration and implementation of the population perspective into relevant science, policies and practice across all four components. Key elements of this approach are the ecologic model of health, principles of population screening, evidence-based decision making, and public health policy and practice that ensures the right balance between "premature translation," leading to increased healthcare costs and potential for harm, and "lost in translation," leading to exacerbation of social, economic and health disparities.

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References

1. Weston AD, Hood L. Systems biology, proteomics, and the future of health care: towards predictive, preventative, and personalized medicine. J. Proteome Res. 2004; 3:179–196. [PubMed: 15113093]
2. Hood, LA.; Zewail, AH., editors. Physical Biology: From Atoms to Medicine. Imperial College Press; London: 2008. p. 337-366.
3. Hood L, Friend S. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol. 2011; 8:184–187. [PubMed: 21364692]
4. Zerhouni, EA. Transforming health: NIH and the promise of research. www.asn-online.org/policy_and_public_affairs/docs/NIH%20in%20the%20post%20doubling%20era.pdf
5. Chakravarti A. Genomics is not enough. Science. 2011; 334:14–15.

6. Collins FS. Shattuck lecture: medical and societal consequences of the human genome project. New Engl J Med. 1999; 341:28–37. [PubMed: 10387940]
7. Green ED, Guyer MS. Charting a course for genomic medicine: from base pairs to bedside. Nature. 2011; 470:204–213. [PubMed: 21307933]
8. Manolio TA, Green ED. Genomics reaches the clinic: from basic discoveries to clinical impact. Cell. 2011; 147:14–16. [PubMed: 21962499]
9. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009; 461:747–753. [PubMed: 19812666]
10. Lupski JR, Belmont JW, Boerwinkle E, et al. Clan genomics and the complex architecture of human disease. Cell. 2011; 147:32–43. [PubMed: 21962505]
11. Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: successful clinical application of the whole exome sequencing in a child with intractable inflammatory bowel disease. Genet Med. 2011; 13(3):255–262. [PubMed: 21173700]
12. St Hilaire C, Ziegler SG, Markello TC, et al. NT5E mutations and arterial calcifications. New Engl J Med. 2011; 364(5):432–442. [PubMed: 21288095]
13. Gwinn M, Grossniklaus DA, Yu W, et al. Horizon scanning for new genomic tests. Genet Med. 2011; 13(2):161–165. [PubMed: 21233720]
14. Moasser MM. Targeting the function of the HER2 oncogene in human cancer therapeutics. Oncogene. 2007; 26(46):6577–92. [PubMed: 17486079]
15. Phillips PA, Marshall DA, Haas JS, et al. Clinical practice patterns and cost-effectiveness of HER2 testing strategies in breast cancer patients. Cancer. 2009; 115(22):5166–5174. [PubMed: 19753618]
16. Gohlke JM, Thomas R, Zhang Y, et al. Genetic and environmental pathways to complex diseases. BMC Syst Biol. May 5.2011 46 PMID 19416532.
17. Frieden TR. A framework for public health action: the health impact pyramid. Am J Publ Health. 2010; 98(9):1543–1544.
18. McGinnis JM. Can medicine and public health partner in the public interest? Health Affairs. 2006; 25:1044–52. [PubMed: 16835185]
19. Khoury MJ, Gwinn M, Burke W, et al. Will genomics widen or help heal the schism between medicine and public health? Am J Prev Med. 2007; 33(4):310–317. [PubMed: 17888858]
20. Feinberg HV. Public health and medicine: where the twain shall meet? Am J Prev Med. 2011; 41(4S3):S149–S151. [PubMed: 21961655]
21. Rockhill B. Theorizing about causes at the individual level while estimating effects at the population level: implications for prevention. Epidemiology. 2005; 16:124–9. [PubMed: 15613957]
22. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985; 14:32–8. [PubMed: 3872850]
23. IOM. Who will keep the public healthy?. National Academy Press; Washington, DC: 2002.
24. Galea S, Riddle M, Kaplan GA. Causal thinking and complex systems approaches in epidemiology. Int J Epidemiol. 2010; 39:97–106. [PubMed: 19820105]
25. Seminara D, Khoury MJ, O'Brien TR, et al. The emergence of networks in human genome epidemiology: challenges and opportunities. Epidemiology. 2007; 18(1):1–8. [PubMed: 17179752]
26. Knoppers BM, Hudson TJ. The art and science of biobanking. Hum Genet. 2011; 130(3):329–332. [PubMed: 21833480]
27. Kho AN, Pacheco JA, Peissig PL, et al. Electronic medical records for genetics research: results of the eMERGE Consortium. Sci Transl Med. 2011; 3(79):79re1.
28. Ioannidis JP, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. Epidemiology. 2011; 22(4):450–456. [PubMed: 21490505]
29. Anonymous. Screening. Epidemiologic Reviews. 2011; 33:1–175. [PubMed: 21709142]
30. Fletcher RH. Screening under scrutiny. Am J Epidemiol. 2011; 174(2):127–128. [PubMed: 21693592]

31. Harris R. Overview of screening: where are we and were we may be headed. Epidemiol Rev. 2011; 33:1–6. [PubMed: 21709142]
32. Barry MJ. Prostate cancer screening: the controversy that refuses to die. New Engl J Med. 2008; 360(13):1351–1354. [PubMed: 19297564]
33. U.S. Preventive Services Task Force. Screening for prostate cancer USPSTF recommendation statement draft. 2011. www.uspreventiveservicestaskforce.org/draftrec3.htm
34. Gulcher J, Stefansson K. Genetic risk information for common diseases may indeed be useful for prevention and early detection. Eur J Clin Invest. 2010; 40(1):56–63. [PubMed: 20055896]
35. Bloss CS, Darst BF, Topol EJ, et al. Direct-to-consumer personalized genomic testing. Hum Mol Genet. 2011; 20(R2):R132–141. [PubMed: 21828075]
36. Harris R, Sawaya GF, Moyer VA, et al. Reconsidering the criteria for evaluating proposed screening programs: reflections from 4 current and former members of the U.S. Preventive Services Task Force. Epidemiol Rev. 2011; 33:20–35. [PubMed: 21666224]
37. Khoury MJ, McCabe LL, McCabe ER. Prinicples of population screening in the age of genomic medicine. N Engl J Med. 2003; 348(1):50–58. [PubMed: 12510043]
38. Fielding JE, Teutsch SM. An opportunity map for societal investments in health. JAMA. 2011; 305(20):2110–2111. [PubMed: 21610244]
39. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. New Engl J Med. 2011; 364:1144–1153. [PubMed: 21428770]
40. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008; 455:1061–1068. [PubMed: 18772890]
41. Hudson TJ, Anderson W, Artez A, et al. International network of cancer genome projects. Nature. 2010; 464:993–998. [PubMed: 20393554]
42. McGuire AL, Burke W. An unwelcome side effect of direct-to-consumer genetic testing: raiding the medical commons. JAMA. 2008; 300(22):2669–2272. [PubMed: 19066388]
43. Burke W, Tarini B, Press N, et al. Genetic screening. Epidemiol Rev. 2011; 33:148–164. [PubMed: 21709145]
44. Evans J, Khoury MJ. Evidence-based medicine meets genomic medicine. Genet Med. 2007; 9(12): 799–800. [PubMed: 18091428]
45. Evaluation of Genomic Applications in Practice and Prevention initiative. www.egappreviews.org
46. Teutsch SM, Bradley LA, Palomaki GE, et al. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP working group. Genet Med. 2009; 11(1): 3–14. [PubMed: 18813139]
47. Khoury MJ, Berg A, Coates R, et al. The evidence dilemma in genomic medicine. Health Affairs (Millwood). 2009; 27(6):1600–1611.
48. Phillips KA. Closing the evidence gap in the use of testing technologies in clinical practice. JAMA. 2008; 3000(21):2542–2544. [PubMed: 19050197]
49. Goosner M. Duke scandal highlights need for genomics research criteria. JNCI. 2011; 103(12): 916–917. [PubMed: 21693754]
50. Ioannidis JP, Khoury MJ. Improving validation practices in “omics” research. Science. in press.
51. Iglehart JK. Prioritizing comparative effectiveness research: The IOM recommendations. New Engl J Med. 2009; 361:325–38. [PubMed: 19567828]
52. Washington AE, Lispstein SH. The patient-centered outcomes research institute: promoting better information, decisions, and health. New Engl J Med. Sep 28.2011 ahead of print.
53. Garber AM, Tunis SR. Does comparative effectiveness research threaten personalized medicine? New Engl J Med. 2009; 360(19):1925–1927. [PubMed: 19420360]
54. Glasgow RE. National Institutes of Health science agenda: a public health perspective. Am J Publ Health. 2007; 97(11):1936–1938.
55. Who will keep the public healthy?. National Academy Press; Washington, DC: 2002. IOM
56. IOM. The future of public health. National Academy Press; Washington, DC: 1986.
57. Khoury MJ, the Genetics Working Group. From genes to public health: the applications of genetic technology to disease prevention. Am J Publ Health. 1996; 86(12):1717–1722.

58. Beskow LM, Khoury MJ, Baker T, Thrasher J. The integration of genomics into public health research, policy and practice in the United States. Comm Genet. 2001; 4(1):2–11.
59. Association for State and Territorial Health Officials. state public health genomics resource guide. 2010. www.astho.org/Programs/Access/Genomics/Genomics/
60. Burke W, Burton H, Hall AE, et al. What should be the agenda for public health in an era of genome-based and "personalized medicine". Genet Med. 2010; 12(12):785–791. [PubMed: 21189494]
61. Khoury MJ, Clauser SB, Freedman AN, et al. Population sciences, translational research, and the promise and challenges for genomics to reduce the burden of cancer in the 21st century. Cancer Epi Biom Prev. 2011; 20(10):2105–2114.
62. McBride CM, Bowen D, Brody LC, et al. Future health applications for genomics: priorities for communication, behavioral, and social sciences research. Am J Prev Med. 2010; 38(5):556–561. [PubMed: 20409503]
63. Kessler R, Glasgow RE. A proposal to speed translation of healthcare research into practice: dramatic change is needed. Am J Prev Med. 2011; 40(6):637–644. [PubMed: 21565657]
64. Wideroff L, Phillips KA, Randhawa G, et al. A health services research agenda for cellular, molecular and genomic technologies in cancer care. Publ Health Genomics. 2009; 12(4):233–244.
65. Khoury MJ, Rich EC, Randhawa G, et al. Comparative effectiveness research and genomic medicine: an evolving relationship for 21st century medicine. Genet Med. 2009; 11:707–711. [PubMed: 19752739]
66. Hamburg MA, Collins FS. The path to personalized medicine. New Engl J Med. 2010; 363(4): 301–304. [PubMed: 20551152]

Table 1

Contributions of the "Population" Perspective to P4 Medicine

	Components of P4 medicine (3)	**Population perspectives**	**Comments**
Predictive	Predicting health using systems approaches based on longitudinal biologic and phenotypic information	Ecologic Model of health	Need to integrate multilevel determinants of health from the macro to the micro using a life-course approach
Preventive	Early disease detection and preventive strategies based on systems approaches	Principles of population screening	Need to evaluate the benefits, harms, costs and societal opportunity of emerging forms of primary prevention and early detection compared to population approaches
Personalized	Targeted therapeutics and diagnostics	Principles of evidence-based medicine	Need to evaluate the benefits, harms and costs of personalized interventions, using formal analytic frameworks, compared to existing treatments, including opportunity costs
Participatory	Educating patients, providers and health systems; building information systems	Essential public health functions (assessment, policy development and assurance); role for population sciences (implementation science; health-services research, comparative effectiveness and regulatory science)	Need to ensure access and equity, develop policies, engage and inform stakeholders; need to collect population-level information on implementation effectiveness, cost effectiveness and unintended consequences