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Personalized Medicine Beyond Genomics: New Technologies, Global Health Diplomacy and Anticipatory Governance

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> "*L'essentiel est invisible pour les yeux*" -- (That which is necessary is invisible to the eyes)
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> • "*Le Petit Prince*" (Antoine de Saint-Exupéry, 1943) [1]

1. INTRODUCTION

Genomics is one of the key technologies enabling personalized medicine and the broader field of theragnostics (i.e., the fusion of therapeutics and diagnostic medicine). Yet other high-throughput technologies (e.g., nanotechnology and proteomics) are also rapidly emerging on the horizon in the postgenomics era since the completion of the Human Genome Project in 2003. Applications of these health technologies, too, are being diversified in personalized medicine. These include both "old" and "new" applications aimed at better understanding host-environment interactions, for example, pharmacogenomics, nutrigenomics (featured in the June and September 2009 issues of the *CPPM*) and pharmacoproteomics, to name a few. Importantly, all these advances are now taking place both "in" and "outside" the traditional laboratory space as personalized medicine innovations diffuse, albeit slowly, from upstream discovery oriented applications (e.g., search for genes associated with common complex diseases) to downstream health products, diagnostics, and personalized interventions in the clinic [2], although not always in that linear direction [3]. Personalized medicine in the postgenomics era calls for a transdisciplinary approach [4], and considerations for how best to develop innovation frameworks to support safe and effective deployment of the new enabling diagnostic technologies.

CPPM aims to address the previously unmet needs in both pharmacogenomics and personalized medicine, for example, by moving beyond the artificial compartmentalization

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of biomarkers and knowledge across health technologies and disciplinary silos. This is crucial as there are important lessons to be learned from different personalized health interventions, whether they involve pharmaceuticals, nutrition, stem cell therapy, or are enabled by genomics, proteomics and nanotechnology. Indeed, these health technologies and their applications can usefully cross-inform each other and thereby help strengthen and triangulate the attendant evidentiary base for personalized medicine. This integrative vision of personalized medicine that includes and extends beyond pharmacogenomics is now being put into practice by the *CPPM* through vigilant and transdisciplinary horizon scanning, and rigorous peer-review with strong international outreach to expertise available in different global regions. Hence, the December issue of the Journal features two new health technologies - nanotechnology and proteomics - that are already beginning to impact the individualization of drug therapy.

2. INTRODUCING THE *CPPM* DECEMBER 2009 ISSUE

When Antoine de Saint-Exupéry's "Le Petit Prince" visits Earth, he meets a fox who presciently exhorts "L'essentiel est invisible pour les yeux" (That which is necessary is invisible to the eyes) [1]. Two-thirds of a century later, the much-needed "invisible" has now been realized in nanotechnology, and more specifically as nanomedical applications that hold great promise for personalized medicine, targeted drug delivery and diagnostic imaging but offer challenges for payers, regulators, patients and global society. In a *CPPM* Feature Article, **Gary Marchant** reminds us that the future of technologies with the potential to fundamentally transform humanity and health care is now, and further explains what we might expect as personalized therapeutics and nanodiagnostics begin to intersect.

In an Interview Article with **Young-Ki Paik**, President of the Human Proteome Organization, we are once again reminded of the postgenomics era – that proteins do matter – diagnostics and targeted interventions that attempt to understand what is happening at a *functional* level may hold more promise than the genome sequences that are their proxies. However, Paik also reminds us that without genomic sequence information, proteomics would face a tremendous barrier in the identification of proteins and their variants involved in disease. Hence, there is much to be gained from tandem applications of pharmacogenomics and pharmacoproteomics in the pursuit of personalized medicine. With the approaching wave of proteomics diagnostics, previous *static* risk assessment frameworks originally developed for familial monogenic diseases will require revision towards a more dynamic, ongoing diagnostic testing *within* the same individual, to obtain a longitudinal "repeated measures" *functional risk* signature (as opposed to between-patient, cross sectional, static, point estimates of risks). This anticipated shift in conceptualization of "health risks" brought about by pharmacoproteomics and advances in postgenomics science and technology will demand novel concepts and mechanisms for regulatory oversight. Additionally, evidence-based analyses of the attendant impacts of pharmacoproteomics on science, medicine and society will be important in order to support and sustain innovations in personalized medicine and theragnostics.

In comparison to rigorous debates held in fields such as anthropology and public health over the past three decades, in-depth reasoned discussions on race-based pharmacogenomics have

not taken place in clinical pharmacology and personalized medicine communities. Understandably, this subject is drawing increasing scrutiny in postgenomics era in parallel to growing international efforts for DNA biobanking and standards in global public health genomics. **Sandra Soo-Jin Lee**, in her *CPPM* Feature Article, presents a timely overview of the newer approaches to identify population genetic differences, including admixture mapping and the use of ancestry informative markers (AIMS), towards controlling population substructure in genetic association studies.

Population pharmacokinetic/pharmacodynamic (PK/PD) analysis was introduced by Beal and Sheiner and the works of other seminal contributors to clinical pharmacology since the 1970s. Population approach to analysis of pharmacology data differs in that it analyzes the entire data of all patients in a population at once, including the cases when there are sparse data obtained in naturalistic real-life clinical settings, or when intensive repeated sampling for PK/PD phenotypes is not clinically feasible. Regrettably, despite their shared focus on "variability questions" concerning drug treatment outcomes, the fields of population PK/PD and pharmacogenomics have remained separate for too long. **Jelliffe *et al***. now initiate a much-needed introduction of population PK/PD modeling to pharmacogenomics and personalized medicine readership. Importantly, they call for more rigorous and quantitative approaches to data analysis in pharmacogenomics that are well informed by fundamental principles of clinical pharmacology study design.

HER2-targeted therapy of breast cancer is often used as a classic example and case study of personalized medicine. However, **Nahta *et al***. appropriately suggest that the work in this subfield of personalized medicine is not yet finished: many patients with HER2-over-expressing metastatic breast tumors do not respond to the monoclonal HER2 antibody trastuzumab or the EGFR/HER2 dual tyrosine kinase inhibitor lapatinib. Their article presents a comprehensive evaluation of personalized medicine for breast cancer by taking into account factors including but beyond HER2 expression.

Fluoropyrimidines such as 5-fluorouracil (5-FU) have been used for decades as cytostatic agents in solid cancer therapy. **Eidens *et al***. present an overview of the human genetic variation in the dihydropyrimidine dehydrogenase (*DPYD*) gene and its clinical predictive value for treatment outcomes with fluoropyrimidine drugs. Importantly, in the spirit of a theragnostics approach to personalized medicine (or 'theranostic', as Eidens *et al*. prefer to articulate), they also emphasize the value of phenotyping for DPYD activity in patients as a complement to genotype based diagnostic tests.

Since its mainstream inception, economic evaluation and cost-effectiveness analysis in particular, increasingly played an ever-important role for payers and those who need to satisfy them, as the cost of bringing technologies to market continues to rise and decision-makers attempt to maximize potential health gains from new technologies with scarce resources. **Daniele Paci** and **Dolores Ibarreta** conduct a thorough examination of the implications pharmacogenetic testing has for those who conduct economic evaluation by examining what has been done to date. They aptly remind us once again that it is what happens before the evaluation that counts – a reminder that good value is difficult to demonstrate with poor or incomplete clinical data.

The theragnostic paradigm does not exist outside of the considerations of payers and policymakers, the technology assessors who support them, and the innovators who must meet their needs, if they wish to be fairly compensated. Innovators who hope to borrow from a pricing paradigm carefully-developed for rare diseases may demand potentially much larger-scale investment on a population-basis. Technologies with superior clinical effectiveness and similar technical efficiency can lead to larger questions of affordability. Although technology assessment frameworks may (or may not) change in the near term, new paradigms for making decisions about large investments at the margins of economic productivity will need to be considered.

In a *CPPM* Symposium Article, **Hızel *et al***. bring to our attention the genomics gap in low- and middle-income countries (LMICs). “Pharmacogenovigilance” is a new hybrid concept discussed by a co-author of the above report (**S. Sardaş**). This term refers to post-marketing surveillance of medication incidents using genetic/genomics screening; a concept that deserves further consideration for potential applications in LMICs. Regional capacity building in LMICs is essential if genomics innovations are to benefit populations and public health globally. But this is no easy task. LMICs suffer from lack of appropriately trained human resources who can evaluate genomics and related health technologies through the lens of global public health. Establishing expertise in postgenomics medicine in LMICs, and supporting the local health researchers who might best understand their own population health care needs are some of the first steps for equitable implementation of pharmacogenomics in global health.

Finally, on behalf of the IUPHAR Clinical Division Sub-Committee on Pharmacogenetics, **Ingolf Cascorbi** sends an open invitation to the personalized medicine community to attend the Pharmacogenetics Workshop at the 16th World Congress on Basic and Clinical Pharmacology (WorldPharma2010) to be held in Copenhagen, Denmark in 2010. WorldPharma2010 (http://www.worldpharma2010.org) is a premier transdisciplinary venue that will bring together the world’s basic and clinical pharmacologists and those concerned with the development and rational use of drugs for a timely discussion on how they can cooperate to meaningfully address the needs for safe and effective medicines at affordable prices.

3. ON THE EDGE OF TOMORROW: HOW BEST TO REGULATE AND SUSTAIN PERSONALIZED MEDICINE INNOVATIONS?

Looking further into the future in 2010 and beyond, we evaluate below several gaps and advances in policy, regulatory science and innovation frameworks that are likely to impact how we utilize emerging health technologies in personalized medicine.

3.1. Proposal For An “Essential Theragnostics Library” in Primary Health Care

Over the past few years, we witnessed the introduction of direct-to-consumer (DTC) whole-genome testing, rapid proliferation of genotype-phenotype association studies, and claims of “theragnostic diagnostics” for a host of complex phenotypes and health outcomes ranging from drug safety, efficacy, response to vaccines and foodstuff to apparently innocuous

human traits, for example, the type of earwax [2]. Opinions on governance of science in the postgenomics era are increasingly polarized. Some commentators emphasize “individual empowerment” through personal genome testing while others advocate for protectionism and tighter regulation. However, as noted aptly by Prainsack *et al*. “protectionism and empowerment are simply different sides of the same governance coin. Both imagine that good governance derives from decisions that are uninfluenced by political and economic forces” [5]. Moreover, postgenomics science and medicine are typified by a highly heterogeneous cast of stakeholders with competing and conflicting interests [2]. In new and rapidly expanding research fields such as genomics and theragnostics, there is an inherent danger that those who administer health services may be unable to distinguish between hype and reality. Conversely, there is also a risk that certain innovations that are ready for prime time can be stifled and fall under “innovation blind spots” due to misdirected precaution and scare-mongering over genuine scientific advances, or disciplinary hyperspecialization endemic in the postgenomics era that can result in “trained incapacity” [6]. The latter is a term coined by economist Thorstein Veblen, referring to acquired blind spots in professions or “learned inability” to maintain a collateral vision or perceive a problem due to extensive specialist training. These complexities of postgenomics medicine, hyperbolic proliferation of claims for predictive diagnostics, and novel configurations of competing/cooperating interest groups in personalized medicine collectively call for independent evaluation of scientific innovations. Put simply, we have a growing need within the personalized medicine and genomics community for new regulatory measures, innovation and socio-ethical frameworks, and independent working groups that can serve an “honest broker” role [9] to evaluate and synthesize impartial evidence on genomics and personalized medicine applications [2, 7–9].

We suggest, in the spirit of the example of the World Health Organization (WHO) Essential Medicines Library, that an “Essential Theragnostics Library” could presumably serve as an integrated regulatory policy measure to objectively evaluate and identify the diagnostics that are ready for prime time applications for preventive diagnosis of population health risks and targeted health interventions (with medicines, food, vaccines, etc.), particularly in primary health care. At this critical juncture when genomics technologies are edging into applications for generic drugs and essential medicines (e.g., consider the recent advances in pharmacogenomics of warfarin, a drug listed in the 2008 WHO Model Formulary), evidence based policy measures such as the creation of an Essential Theragnostics Library would contribute towards affordable and equitable access to diagnostics. For health, we need access not only to medicines and other interventions but also to companion diagnostics.

We note that personalized medicine and genomics need not necessarily be in a conflict with the population health mandate in developed or developing countries. While personalized medicine applications can result in targeted interventions for a subpopulation that share a certain genomic signature (i.e., not for individual persons), these interventions are based on prior testing of the genomics factors in the entire population. This can benefit not only the subpopulations who may receive a medicine with a modified therapeutic regimen based on genomic variation, but also the rest of the population who may otherwise not have access to a drug when, for example, a drug is withdrawn from the clinic because predictive tests for a serious drug toxicity is not available. We do not underestimate, however, that such an

undertaking can be an enormous challenge in practice. A proof of concept study of this potential regulatory policy tool in carefully selected therapeutic areas that have high priority for global public health could presumably be a first step to assess its feasibility.

3.2. Global Health Diplomacy: A Hybrid Field In The Making - With Relevance For Health Technology Innovation Policy

It used to be that diplomacy was reserved for “hard issues” that relate to war and peace or economy and trade. This is no longer the case. Health is increasingly seen as an integral part of diplomacy and foreign policy with hard impacts, for example, on international access to medicines and management of global outbreaks of disease and pandemics. Rapid international adoption of genomics technologies, enabled in part by reduced cost of genotyping and whole-genome sequencing, is creating cross-cutting health care, public health and policy issues that transcend the national borders and require action at the level of global health. Chief among these emerging issues is the need for joint expertise in health, foreign policy and diplomacy. Kickbusch *et al.* recently observed that “global health diplomacy is gaining in importance and its negotiators should be well prepared. Some countries have added a full-time health attaché to their diplomatic staff in recognition of the importance and complexity of global health deliberations; others have added diplomats to the staff of international health departments. Their common challenge is to navigate a complex system in which issues in domestic and foreign policy intertwine the lines of power and constantly influence change, and where increasingly rapid decisions and skilful negotiations are required in the face of outbreaks of disease, security threats or other issues” [10].

An important contributor to global health diplomacy is Brazil where health is a right of the people and an obligation of the Brazilian state, as outlined in the Brazilian constitution. Close cooperation between the Brazilian Ministry of Foreign Affairs and the Ministry of Health has played a pivotal role on global policy for access to antiretroviral drugs for HIV/AIDS [10]. Looking further, it is conceivable that global health and diplomacy will continue to intersect in relation to access to diagnostics, adoption of personalized health interventions and their affordable pricing. Global health diplomacy is a hybrid field in the making, and a potential (but presently overlooked) tool for international policy-making in health care and biomedicine. It is also a good testament that postgenomics science takes place both inside and outside the laboratory space. Because personalized medicine and genomics- and proteomics-based diagnostic technologies are now being utilized in biomedical research both in the developed and developing world, health care innovation frameworks require global consideration. These policy development mechanisms require multiple levels of science governance including both domestic and foreign policy. The new concepts of global health diplomacy and Essential Theragnostics Library are also connected; both will require international cooperation and action towards global health beyond a narrow focus on national health care policy. What happens abroad affects the local and regional contexts and vice versa.

3.3. Anticipatory Governance and Real-Time Monitoring of Innovations: Lessons From The Cold War Era For Personalized Medicine

As we present both nanotechnology and proteomics in the present issue of the Journal, we need to bear in mind that the future is yet undecided; the availability of a new technology does not necessarily guarantee its successful uptake towards personalized medicine. New health technologies have both intended and unintended impacts on science, medicine and society. Moreover, postgenomics medicine increasingly recognizes the concept of plasticity particularly in empirically driven new fields of inquiry such as systems biology and epigenetics - genes are now conceptualized as hereditary units highly responsive to their environment instead of rigid genetic currencies. Hence, we need new approaches to health technology assessment and policy-making that better reflects the dynamic nature of the postgenomics science itself [11, 12].

Anticipatory governance (AG) is a new concept that has substantial relevance for policy-making and health technology assessment. AG has its origins in part in the public administration literature. Chi explains anticipatory governance as “changing short-term-oriented decision-making practices to longer-term policy making with vision and foresight. This allows legislative, management, and adjudication processes to be based more on informed trends and fact and evidence-based decisions as well as preferred futures *designed together* by state officials and citizens” [13]. Importantly, AG can permit “co-cultivation” of socio-technical futures jointly by experts and citizens, rather than waiting until the attendant regulatory, economic, social or ethical impacts explode into a crisis. This could also encourage scientists to be more aware of, and responsive to social, political and ethical consequences of their own research.

Because multiple factors (some of which are unknowable beforehand) shape the evolution of a new technology, there will be limits to the extent that we can anticipate their future trajectory and impacts. Real-time monitoring (RTM) is a concept left over from the cold war era when there were two competing super powers in global politics [13]. While an AG framework can facilitate us to “think the unthinkable”, this can also lead to an undesirable “inflation of the futures” regarding new technologies. What is needed is an approach that can endorse AG while “calibrating” and fine-tuning predictions made by AG through RTM of the *actual* trajectories of a technology using empirical methods. We suggest that the AG/RTM approach can bring about foresight and further ground such anticipatory outlook through real-time analyses of emerging health technologies. AG/RTM framework thus provides a longitudinal temporal framework to analyze the innovation ecosystems in personalized medicine.

The concept of AG/RTM is not only limited to emerging sophisticated health technologies but has broad implications for medicine and post-marketing vigilance of health interventions that are more traditional and less technologically oriented. A case in point is the lessons learned from reducing risk of harmful medication incidents with concentrated potassium chloride solutions. For example, ISMP Canada, through an AG strategy, led the movement in Canada to remove *concentrated* potassium chloride solutions from patient care areas in hospitals to reduce the risk of its inadvertent injection (a potentially fatal error). The anticipated fundamental human errors were errors of substitution -ampoules and vials of

concentrated potassium chloride closely resemble other products such as sodium chloride 0.9%, and sterile water, i.e., look-alike health products. Use of ready-to-use pre-mixed dilute solutions with potassium chloride and standardized prescribing practices were promoted to support a change initiative. However, during the RTM of these implemented changes to amend the medication use systems in hospital care, both anticipated and unanticipated impacts became apparent. Some unanticipated reactions to this initiative included: (i) resistance among hospital staff questioning the need for change, (ii) inappropriate storage of the concentrated potassium chloride solution when change management was not optimal. Nonetheless, in 2007 the WHO Collaborating Centre for Patient Safety Solutions published suggested actions for control of concentrated electrolyte solutions and cited initiatives such as those in Canada, indicating wide support [14]. Accrediting organizations in different countries now mandate control of concentrated electrolytes. Such actions are an extension of the AG/RTM approach initiated by ISMP and other safety organizations. With system improvement initiatives, including the emerging health technologies in postgenomics medicine, there is a need for proactive risk/benefit assessment. There is also a need for RTM that extends for a suitable long time frame in order to identify and respond to unexpected/unintended impacts.

4. CONCLUDING REMARKS

In an interview in 1992, Lewis B. Sheiner, a seminal contributor to study of population variability in response to medicines, commented “to be productive, scientists need to keep their eye on the ball, on the problem, which is understanding the subject matter better or teaching students better. Then everything else falls out; they become successful as a researcher, or successful as a teacher, and get the rewards. But they should not keep the rewards in mind as the reason for it” [15]. This sentiment resonates even more true these days when we need to constantly sort out the facts through a pile of genomics data in personalized medicine while keeping in mind the age-old maxim in rational therapeutics: “*treat the patient and not the laboratory test*” [4].

Original founders of the field of pharmacogenetics in the 1950s had access to a much fewer set of technologies. Instead, they employed astute observations and evidence collected by less advanced technologies that revealed, however, fundamental mechanisms in biology and clinical pharmacology [16]. “Keeping the eye on the ball” in personalized medicine in the postgenomics era thus entails asking how a new technology or genomics test will inform our understanding of variable human and population responses to medicines, and how that mechanistic understanding, in return, might usefully inform how we treat individual patients [4], and address population health risks [7, 9, 17].

As we continue to evaluate emerging technologies, we need to recall that truly novel innovations may not reach the popular mainstream immediately. In fact, one could perhaps suggest that a good number of original ideas start out (and remain) in the fringes. Innovation is not always a popularity contest whether it is in academia, private sector or performing arts [18]. Truly original concepts that fundamentally break from the past traditions can remain in obscurity, misrepresented through one-sided critique and professional hyper-jealousy, or rejected outright by existing conceptual frameworks. Innovations tend to be cultivated by

crystallization of intellectual entropy in the middle of chaos: that is, at the intersection of new ideas that struggle for survival and future representation on the one hand, and antagonism by existing ideas, institutionalized forms of old knowledge, and human and nonhuman actors in science and society whose power structures may be disrupted by innovations and novel ways of human understanding. This may apply to ideas that offer both incremental (evolutionary) or fundamental (revolutionary) advances from the past models. Understanding of the nature of innovations (and of innovators' dilemma) is essential if we do not want to miss out novel ideas that can benefit how we conceive and implement personalized medicine.

It would be a naive mistake to think that the future of innovations can be "predicted" entirely or fully governed *a priori*. We prefer to use the term '"anticipation" as this would acknowledge the role of serendipity inherent to scientific innovations [16]. Still, it is possible to "cultivate" a foreground that can better anticipate the future of certain technology applications where similarities of the technology (e.g., pharmacogenomics and pharmacoproteomics) can help cross-inform each field. Yet the dissimilar aspects of such fields also demand real-time empirical monitoring (i.e., RTM) of the anticipated futures so that what is anticipated can be further calibrated as the technologies evolve.

Pharmacogenomics cannot succeed with access to biotechnology alone. It also demands competence in pharmacology study design and sound interpretation of its applications to clinical therapeutics and postgenomics biology. As a traditional laboratory-based discipline, pharmacology has so far neglected (sadly) the social drivers and impacts of pharmaceutical sciences in the past, with the exception of a few academic centers [19]. To the extent that drugs will always have undeniable social, ethical, legal, political and economic components (and consequences), further advances for conceptual frameworks in social pharmacology are essential. This means that the traditional pharmacology laboratory "bench space" has to expand to society, and take into account, for example, how data translates into knowledge and the socio-ethical factors that can facilitate, hinder or bias this knowledge translation process. While the emerging field of social pharmacology may offer guidance in these aspects, it still requires integration with the recent empirical turn in philosophical bioethics towards evidence-based ethics. This could bring greater support and credibility for claims made in and by bioethics and social pharmacology, as they face the complex realities of postgenomics technology and medicine in the near future [12].

The human condition, in facing the future, inevitably experiences hope, fear, and uncertainty. These motives often drive research and development, creativity, financial investments and action, not only in science and medicine, but also in global political realities that firmly impact international health. Indeed, emerging technologies conjure up hope, fear and other forms of potentialities in collective imaginations. Hence, as we look into 2010 and beyond, we need to recognize that the future is not an empty slate but tends to be colonized by multiple potentialities that are often contested and highly politicized. Yet pressures to be more responsive to the future of new technologies - particularly while the regulatory and innovation landscape is still rapidly shifting - remains a reality of the 21st century science. The road ahead in personalized medicine and pharmacogenomics is arduous but one whose products will markedly impact the practice of science and medicine in global society.

Thinking outside the outdated master narratives of science and technology is essential if we are to make long term progress that benefits population health and stand the test of time, rather than a narrow focus on technology, immediacy or short term gains that cannot be sustained. We trust that the newer innovation frameworks, regulatory and policy-making concepts presented in this editorial outlook might usefully inform our readers in the field of pharmacogenomics and personalized medicine.

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References

1. Saint-Exupéry, A. Le Petit Prince. Orlando: Harcourt, Inc; 1943.
2. Ozdemir V, Suarez-Kurtz G, Stenne R, et al. Risk assessment and communication tools for genotype associations with multifactorial phenotypes: the concept of “edge effect” and cultivating an ethical bridge between omics innovations and society. OMICS. 2009; 13(1):43–61. [PubMed: 19290811]
3. Guston DH. Innovation policy: not just a jumbo shrimp. Nature. 2008; 454(7207):940–1. [PubMed: 18719568]
4. Ozdemir V, Someya T. A transdisciplinary forum for study of individual and population variability in response to health interventions and personalized medicine. Curr Pharmacogenomics Person Med. 2009; 7(3):146–8.
5. Prainsack B, Reardon J, Hindmarsh R, et al. Personal genomes: misdirected precaution. Nature. 2008; 456(7218):34–5. [PubMed: 18987720]
6. Veblen, T. The Instinct of Workmanship and the State of the Industrial Arts. New York: Macmillan; 1914.
7. Burke W, Khoury MJ, Stewart A, et al. The path from genome-based research to population health: Development of an international public health genomics network. Genet Med. 2006; 8:451–8. [PubMed: 16845279]
8. Teutsch SM, Bradley LA, Palomaki G, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP working group. Genet Med. 2009; 11:3–14. [PubMed: 18813139]
9. Khoury MJ. Interview: Dr. Muin J. Khoury Discusses the Future of Public Health Genomics and Why It Matters for Personalized Medicine and Global Health. Curr Pharmacogenomics Person Med. 2009; 7(3):158–63.
10. Kickbusch I, Silberschmidt G, Buss P. Global health diplomacy: the need for new perspectives, strategic approaches and skills in global health. Bull World Health Organ. 2007; 85:230–2. [PubMed: 17486216]
11. Knoppers BM. Genomics and policymaking: from static models to complex systems? Hum Genet. 2009; 125(4):375–9. [PubMed: 19252928]
12. Ozdemir V. What to do when the risk environment is rapidly shifting and heterogeneous? Anticipatory governance and real time assessment of social risks in multiply marginalized populations can prevent IRB mission creep, ethical inflation or underestimation of risks. Am J Bioethics. 2009; 9(11):65–8.
13. Chi, KS. Four strategies to transform state governance. Washington, DC: IBM Center for the Business of Government; 2008.
14. World Health Organization Collaborating Centre for Patient Safety Solutions. Control of Concentrated Electrolyte Solutions. Volume 1, Solution 5. 2007Accessed Nov 9 2009Available from: http://www.ccforpatientsafety.org/common/pdfs/fpdf/presskit/PS-Solution5.pdf

15. James JS. Clinical Trials: Asking the Right Questions -- Interview with Lewis Sheiner, M.D. AIDS Treatment News. 1992 Jan 7.:142.

16. Easton M. Great discoverers - Defining a discipline. Werner Kalow, “father of pharmacogenetics”. 2002Accessed November 9, 2009Available from: http://www.research.utoronto.ca/edge/fall2002/discover.html

17. Zimmern RL. Testing challenges: evaluation of novel diagnostics and molecular biomarkers. Clin Med. 2009; 9:68–73.

18. Kozinn A. Obituary. John Cage, 79, a minimalist enchanted with sound, dies. The New York Times. 1992Accessed November 9, 2009Available from: http://www.nytimes.com/learning/general/onthisday/bday/0905.html

19. Montastruc JL. Social pharmacology: a new topic in clinical pharmacology. Therapie. 2002; 57:420–6. [PubMed: 12611195]