



The future may be closer than you think: a response from the Personalized Medicine Coalition to the Royal Society's report on personalized medicine

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A recent report from the British Royal Society on the prospects for personalized medicine provides a sobering assessment of the field and its prospects. The report contends that pharmacogenetics has little clinical relevance at the moment and will only progress with the completion of large, cumbersome clinical trials. The report goes on to note that the regulatory infrastructure, medical education initiatives and public deliberation necessary to make personalized medicine a reality are essentially nonexistent, at least so far. In our view, personalized medicine is much more than a hypothetical protocol designed to correlate genotypes with prescriptions. We argue that the development of personalized medicine is a broader phenomenon that is already being practiced in one form or another in many contexts. Both academic medicine and the pharmaceutical industry have a huge stake in bringing pharmacogenetic-based personalized medicine to fruition; we expect both entities to act as drivers of what will be a long-term, iterative process.

Recently, the British Royal Society produced a 50-page assessment of the field of pharmacogenetics, entitled "Personalised Medicines: Hopes and Realities" [101]. The report offers a thorough review of the state of our art: it discusses the history of medical genetics and pharmacogenetics, pharmacological principles, how drug development works, clinical applications of pharmacogenetics, emerging ethical issues and the outcome of public dialog on the subject in Britain. In this commentary, we address specific conclusions reached by the authors of the report and perhaps offer a somewhat more optimistic view of the future of personalized medicine.

The prevailing message of the report is best exemplified by its contentions that pharmacogenetics has a negligible impact on current clinical practice, and is unlikely to revolutionize or personalize medical practice in the near future [101]. Few would take issue with either point. However, if we step back and broaden our terms, it becomes evident that the personalization of medicine is already well under way. For example, by the report's own admission, physicians regularly titrate dosages in order to optimize their patients' responses to drugs such as warfarin. In addition, every day primary care doctors use the Framingham Risk Score to stratify patients into different categories of 10-year risk for cardiac events in order to recommend appropriate lifestyle and therapeutic strategies [1]. These may not qualify as high-tech pharmacogenetics, but they are real manifestations of personalized medicine nonetheless.

More to the point, the evolving paradigm these crude examples support is one of risk stratification based substantially on genotype, albeit indirect measures of genotype. The new personalized medicine, as exemplified by direct correlation of genotype with drug response, dosage, disease state and/or prognosis, is merely a step further along a continuum of care that is already established. The key question is how quickly we can make the transition from the indirect to the direct. In some cases, particularly for diseases such as diabetes and obesity, it may indeed take decades. But when, for example, gene expression signatures with predictive value are recognized for their potential clinical utility in diffuse large B-cell lymphomas [2], acute myeloid leukemias [3,4], breast cancer [5-9], and even cardiovascular disease [10], the future may be closer than we think.

We would also emphasize that direct genotypic and gene expression measures are not the only toolsets available to practitioners of personalized medicine. DNA microarrays are, but one, 'omics' technology that can be considered almost ready for primetime; protein biomarkers appear to be on the near-term horizon for personalized medicine as well. The use of troponin in the detection of cardiac injury is a recent and impressive example of protein biomarker technology as a tool to offer personalized evaluations of one of our major public health scourges [11,12]. Troponin itself is part of a long, evolving line of cardiac biomarkers, from lipids to creatine kinase to C-reactive protein, that are now part of the

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practitioner's common vernacular to assess risk and guide therapy for the individual patient. What all such markers have in common is that to a large extent they are reflections of patients' genomes; they are, after all, gene products produced in response to environmental stimuli.

The report also states that clinical trials will be necessary before new pharmacogenetic tests can be brought to market. Again, it is an obvious and valid point. Prospective trials are a prerequisite to determining whether pharmacogenetic testing consistently leads to the selection of the right drugs and doses for individual patients, thereby improving therapeutic responses while reducing adverse ones [13]. While such trials may not be feasible when the genetic or genomic variants of interest are rare, they should be well within our reach for assessing the power of more common variants.

Ultimately, clinical trials must begin upstream. For its part, the report acknowledges that pharmacogenetics is likely to become increasingly critical to the drug discovery and development process. In fact, this has already occurred. Until recently, one might have argued that the pharmaceutical industry has no incentive to segment its target populations via pharmacogenetics and thereby reduce the size of its market for presumptive blockbusters. However, in the wake of high-profile adverse reactions to rofecoxib (Vioxx®) and other cyclooxygenase (COX)-2 inhibitors, such arguments are no longer valid [14].

Even before the Vioxx fiasco, the private sector had begun to demonstrate a willingness to incorporate pharmacogenetic criteria in the development process. Trastuzumab (Herceptin®) in the treatment of breast cancer guided by Her-2/Neu testing, and imatinib mesylate (Gleevec®) for the treatment of chronic myeloid leukemia diagnosed by the presence of the breakpoint cluster region-abelson (bcr-abl) fusion protein, are perhaps the most notable examples of products for which use is indicated only in the presence of a specific biomarker [15]. In many cases, the initially smaller markets of patients defined by biomarkers have been expanded as further disease indications are discovered for patented drugs. Now, several major pharmaceutical companies are considering such strategies *a priori*: they are targeting small populations with rare genetic diseases in the hope they can drastically cut the duration of clinical trials and later expand the use of branded therapies to treat related indications [16]. Clearly, cancer is well ahead of other chronic diseases in terms of the application of this paradigm.

Further evidence that the pharmaceutical industry is willing to include pharmacogenetic testing as part of clinical development can be gleaned from the fact that more than 25 programs containing such data are currently before the US FDA as voluntary genomic data submissions [Felix Frueh. PERS. COMMUN.]. Moreover, several academic groups have begun to explore the development of pharmacogenetic tests on already-marketed drugs [17,18]. Again, cancer is the best opportunity for such tests; other common diseases may require greater numbers of markers, larger populations and longer time frames. Ultimately, the clinical utility of pharmacogenetics and personalized medicine, for cancer and everything else, will occur only through the combined efforts and pooled resources of industry, regulators and academia.

These developments speak to the emergence of regulatory standards in pharmacogenetics, which is cited as another necessary factor for success in the Royal Society report. Ironically, in the USA the regulatory climate *vis-à-vis* pharmacogenetics may actually be outpacing private-sector technological initiatives in the field. Within the last few years, for example, the US FDA has:

- Developed voluntary guidance for pharmacogenetic data submissions [102]
- Explicitly acknowledged the relationship between genotype and response to multiple drugs [19]
- Approved the first device for rapid diagnostic genotyping of more than 30 pharmacogenetically relevant variants in two cytochrome P450 (*CYP*) genes [20]
- Announced an agreement to collaborate with the National Cancer Institute and the Centers for Medicare & Medicaid Services on improving the development of cancer therapies and the outcomes for cancer patients through biomarker development and evaluation [103]

Whether these initiatives will be sufficient to create the necessary regulatory infrastructure remains to be seen – but it's a promising start.

Another hurdle is cost. Cost-benefit analyses in personalized medicine initiatives will need to be performed on a case-by-case basis, according to the report. Thus far, genetic and genomic cost analyses have been slow in coming, but hardly absent. Since 1996, at least 149 economic analyses of genetic services have been conducted, mostly for adult conditions such as cancer [21].

Few studies have analyzed pharmacogenomic testing *per se*, but those that have been performed have largely indicated these tests to be

cost effective [22,23]. In particular, when a genomic biomarker assay can be conducted on a serum or urine sample and replace an assay requiring a tissue sample obtained through a biopsy, cost savings may be substantial. For example, the molecular profiling assay to identify heart transplant patients at risk for rejection has been shown to be cost effective compared with the standard procedure of endomyocardial biopsy [24].

Elsewhere, several studies of single-locus genetic testing for thiopurine methyltransferase (*TPMT*) deficiency, which can lead to severe toxicities in patients treated with purine drugs, have found such testing to be cost-beneficial under certain conditions [25–29]. The Royal Society report also makes this point [101]. We would argue that even if *TPMT* testing itself never becomes widespread (and for a number of reasons we believe it probably will not), these studies offer evidence that the economic constraints of personalized medicine can be addressed and that such analyses can provide the data necessary to make painful decisions regarding the allocation of care. In our view, it's time for more US academic scientists and healthcare economists to bring their collective expertise to bear in order to fill this knowledge gap.

Perhaps the most urgent call to action made in the Royal Society report – and possibly the one most critical to the successful furtherance of pharmacogenetics in the USA – is the need for education, especially among healthcare professionals [30]. Given the rapid evolution of the field, coupled with the possibility that adverse drug reactions may represent the sixth (or worse) leading cause of death among hospitalized patients [31], the need for pharmacogenetically enlightened medical education will only become more acute as time passes. To its credit, the US FDA appears to have recognized the gap in genetics education [32]. We wish the same could be said for the US academic medical education establishment. Of course, our concern is hardly limited to current and future physicians: a concerted effort is also needed to educate the general public – the adoption of personalized medicine will only occur following acceptance by society as a whole. Even in Iceland, where the public has

largely signed on to the efforts of the firm deCODE Genetics (Reykjavik, Iceland) to collect DNA and health information on most of the island's adult population, debate has been vigorous and sometimes fractious [33].

Despite its sometimes dour tone, the Royal Society report ultimately succeeds in conveying the bigger picture: personalized medicine will be a long-term proposition – to do it effectively will take time. Prospective pharmacogenetic trials for any number of conditions – cancer, cardiovascular disease and Alzheimer's disease, to name just a few – will require years to adequately measure outcomes. For non-Mendelian conditions other than cancer, where tissue is often inaccessible, the challenges will be especially formidable. We should set our expectations accordingly.

Having said that, in our view the environment for personalized medicine is an encouraging one. The FDA has displayed significant leadership on regulatory and educational aspects of the issue and a number of trials are under way. The drug industry appears to recognize that pharmacogenetics can not only help avoid safety issues and their accompanying liabilities, but may also lead to the design of targeted, less toxic and more efficacious therapies. Meanwhile, academic medicine, in its pursuit of evidence-based treatment, is beginning to utilize genetic and genomic measures in a therapeutic context, not only because it's the right thing to do for patients, but because it's the approach for which translational researchers will be rewarded by funders. If that was not explicit before, the National Institutes of Health (NIH) Roadmap has since made it crystal clear [34].

For personalized medicine to be a success, every institution involved in biomedical research and healthcare delivery – be it public, private or regulatory – must be engaged and committed to the process. If that happens, hopes may yet become realities.

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Highlights

- The British Royal Society recently released a thorough, but somewhat pessimistic report on the prospects for personalized medicine.
- The authors contend that personalized medicine is not necessarily a discrete phenomenon, but rather part of a continuum of clinical care that has already begun to take hold.
- Personalized medicine's first major impact will likely be in the field of cancer, where gene expression profiling is expected to radically alter prognostic and therapeutic approaches in the near future; protein biomarkers may do the same for cardiovascular disease, although the time frame may be longer.
- Recent high-profile adverse drug reactions point to the need to integrate pharmacogenetics into the drug development process; the pharmaceutical industry has already begun to embrace this idea.
- The US FDA appears to be ahead of the curve with respect to regulation of pharmacogenetics, although much remains to be done.
- Cost will be a major inflection point for the development of personalized medicine. A number of cost-benefit analyses have been conducted, but more and larger ones must be carried out in conjunction with large clinical trials.
- Education – of healthcare professionals and the general public – will be a critical prerequisite for the realization of personalized medicine.
- The National Institutes of Health's emphasis on translational medicine promises to further drive the development of personalized healthcare now and in the future.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Anthony D: Diagnosis and screening of coronary artery disease. *Prim. Care* 32, 931–946 (2005).
2. Sweetenham JW: Diffuse large B-cell lymphoma: risk stratification and management of relapsed disease. *Hematology (Am. Soc. Hematol. Educ. Program)* 252–259 (2005).
3. Valk PJ, Verhaak RG, Beijin MA *et al.*: Prognostically useful gene-expression profiles in acute myeloid leukemia. *N. Engl. J. Med.* 350, 1617–1628 (2004).
4. Bullinger L, Dohner K, Bair E *et al.*: Use of gene-expression profiling to identify prognostic subclasses in adult acute myeloid leukemia. *N. Engl. J. Med.* 350, 1605–1616 (2004).
- **References 3 and 4 are two prime examples of how gene expression can alter the approach to prognostics in oncology.**
5. Lonning PE, Sorlie T, Borresen-Dale AL: Genomics in breast cancer – therapeutic implications. *Nature Clin. Pract. Oncol.* 2, 26–33 (2005).
6. Murphy N, Millar E, Lee CS: Gene expression profiling in breast cancer: towards individualising patient management. *Pathology* 37, 271–277 (2005).
7. Nevins JR, Huang ES, Dressman H *et al.*: Towards integrated clinico-genomic models for personalized medicine: combining gene expression signatures and clinical factors in breast cancer outcomes prediction. *Hum. Mol. Genet* 12(Spec. No 2), R153–R157 (2003).
- **Gene expression-based prognostics taken one step further by integrating clinical indicators with microarray data.**
8. Paik S, Shak S, Tang G *et al.*: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N. Engl. J. Med.* 351, 2817–2826 (2004).
9. van de Vijver MJ, He YD, van't Veer LJ *et al.*: A gene expression signature as a predictor of survival in breast cancer. *N. Engl. J. Med.* 347, 1999–2009 (2002).
10. Liew CC: Expressed genome molecular signatures of heart failure. *Clin. Chem. Lab. Med.* 43, 462–469 (2005).
11. Newby LK, Goldmann BU, Ohman EM: Troponin: an important prognostic marker and risk-stratification tool in non-ST-segment elevation acute coronary syndromes. *J. Am. Coll. Cardiol.* 41, 31S–36S (2003).
12. Babuin L, Jaffe AS: Troponin: the biomarker of choice for the detection of cardiac injury. *CMAJ* 173, 1191–1202 (2005).
13. Eichelbaum M, Ingelman-Sundberg M, Evans WE: Pharmacogenomics and individualized drug therapy. *Annu. Rev. Med.* 57, 119–137 (2006).
14. Lewis R: An individual approach. *Nature* 436, 746–747 (2005).
15. Newell DR: How to develop a successful cancer drug – molecules to medicines or targets to treatments? *Eur. J. Cancer* 41, 676–682 (2005).
16. Penny MA, McHale D: Pharmacogenomics and the drug discovery pipeline: when should it be implemented? *Am. J. Pharmacogenomics* 5, 53–62 (2005).
- **Thoughtful reflection on how and when to integrate pharmacogenomics into the drug development process.**
17. Grice GR, Seaton TL, Woodland AM *et al.*: Defining the opportunity for pharmacogenetic intervention in primary care. *Pharmacogenomics* 7, 61–65 (2006).
18. Sequist LV, Haber DA, Lynch TJ: Epidermal growth factor receptor mutations in non-small cell lung cancer: predicting clinical response to kinase inhibitors. *Clin. Cancer Res.* 11, 5668–5670 (2005).
19. Need AC, Motulsky AG, Goldstein DB: Priorities and standards in pharmacogenetic research. *Nature Genet.* 37, 671–681 (2005).
- **An important reminder that drug response is a complex trait requiring careful analysis of phenotypes and systematic representation of genetic variation.**
20. Jain KK: Applications of AmpliChip™ CYP450. *Mol. Diagn.* 9, 119–127 (2005).
21. Carlson JJ, Henrikson NB, Veenstra DL *et al.*: Economic analyses of human genetics services: a systematic review. *Genet. Med.* 7, 519–523 (2005).
22. Phillips KA, Van Bebber SL: Measuring the value of pharmacogenomics. *Nature Rev. Drug Discov.* 4, 500–509 (2005).
- **The authors apply a resource-allocation framework to pharmacogenomics and demonstrate the huge potential medical and economic benefits that could accrue from expanding the use of pharmacogenomics. They also warn that those benefits won't be realized without analysis and dissemination of much larger datasets.**
23. Hornberger J, Cosler LE, Lyman GH: Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. *Am. J. Manag. Care* 11, 313–324 (2005).
24. Deng MC, Eisen HJ, Mehra MR *et al.*: Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am. J. Transplant* 6, 150–160 (2006).

25. Tavadia SM, Mydlarski PR, Reis MD *et al.*: Screening for azathioprine toxicity: a pharmaco-economic analysis based on a target case. *J. Am. Acad. Dermatol.* 42, 628–632 (2000).
26. Marra CA, Esdaile JM, Anis AH: Practical pharmacogenetics: the cost effectiveness of screening for thiopurine S-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. *J. Rheumatol.* 29, 2507–2512 (2002).
27. Oh KT, Anis AH, Bae SC: Pharmaco-economic analysis of thiopurine methyltransferase polymorphism screening by polymerase chain reaction for treatment with azathioprine in Korea. *Rheumatology (Oxford)* 43, 156–163 (2004).
28. Clunie GP, Lennard L: Relevance of thiopurine methyltransferase status in rheumatology patients receiving azathioprine. *Rheumatology (Oxford)* 43, 13–18 (2004).
29. Dubinsky MC, Reyes E, Ofman J *et al.*: A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Am. J. Gastroenterol.* 100, 2239–2247 (2005).
30. Frueh FW, Gurwitz D: From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenomics* 5, 571–579 (2004).
31. Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 279, 1200–1205 (1998).
32. Frueh FW, Goodsaid F, Rudman A *et al.*: The need for education in pharmacogenomics: a regulatory perspective. *Pharmacogenomics J.* 5, 218–220 (2005).
- **The authors argue, logically, that pharmacogenomics will never penetrate the marketplace if its would-be purveyors do not fully understand it.**
33. Abbott A: Icelandic database shelved as court judges privacy in peril. *Nature* 429, 118 (2004).
34. Zerhouni EA: US biomedical research: basic, translational, and clinical sciences. *JAMA* 294, 1352–1358 (2005).

Websites

101. The Royal Society: Personalised medicine: hopes and realities. www.royalsoc.ac.uk/displaypagedoc.asp?id=15874
- **A thorough assessment of the current state of pharmacogenetics and future prospects for incorporating genomic information into clinical medicine, with special reference to the UK.**
102. Genomics at US FDA webpage. www.fda.gov/cder/genomics/default.htm
103. US Department of Health and Human Services press release: New Federal Health Initiative to Improve Cancer Therapy. www.fda.gov/bbs/topics/news/2006/NEW01316.html