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MEETING REPORT

Personalized Medicine Europe: Health, Genes and Society: Tel-Aviv University, Tel-Aviv, Israel, June 19–21, 2005

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Personalized medicine: time for some tough questions

The workshop 'Personalized Medicine Europe: Health, Genes and Society', cosponsored by the European Science Foundation and the Yoran Institute for Human Genome Research at Tel-Aviv University, Sacker Faculty of Medicine, was held at the Tel-Aviv University campus on June 19–21, 2005. The concept of '*Personalized Medicine*' marks the expected reform in medicine that is projected to arrive at the clinic in coming decades, harnessing genomics and proteomics technologies for tailoring the most suitable pharmacotherapy for the each patient, based on individual profiling ([1–4]; see also list of 'selected web resources on personalized medicine'). There are high expectations for better pharmacotherapy, allowing drastic reductions in the current alarmingly high rates of adverse drug reactions, accounting to almost 7% of new hospital admissions.[5,6] Personalized medicine is also projected to allow improved treatment efficacies for many diseases. Following the recent success of drug tailoring in oncology with the aid of genomic and proteomic tools, there have been high public expectations for better diagnostic tools to improve treatment outcomes in other fields of medicine. Along with these expectations for improved safety and efficacy in pharmacotherapy, there is a rising anxiety that the arrival of genomic and proteomic technologies to the clinic might jeopardize equity in healthcare, a key principle for national health services of the modern state. Some critics argue that the expectations are too high, given the huge complexity of the human genome and proteome.[7] Moreover, new studies suggest that while genes often contribute to disease phenotypes, they are far from determining them. The old question of *Nature or Nurture* is not about to be solved soon, and moreover, it becomes clear that with few exceptions, genes alone cannot be blamed for failure of drug treatments.

The Tel-Aviv workshop in June 2005 served as a stage for presenting and discussing such new knowledge, at the forefront of science and medicine, along with discussions on societal and ethical implications of this newly gained information. Many questions were raised; some were discussed following the presentations and during the panel discussion on the closing session; most issues remained open, without reaching a consensus. However, asking the right questions is the first and essential step in looking for tentative solutions; in that respect, we hope that the 'right questions' about personalized medicine were indeed raised so that we can continue the quest for the best answers.

The workshop lasted 3 full days and consisted of 40 invited presentations, six oral poster presentations by graduate and post-graduate students (selected among 14 posters on display), and a concluding panel discussion. As its name implies, the workshop was primarily designed for a multidisciplinary exchange of views, examining basic biological and clinical, as well as ethical and societal aspects of pharmacogenetics. The rapidly evolving field of pharmacogenetics has its roots almost 50 years ago,[8] but is

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evolving rapidly since the completion of the Human Genome Project and the realization of the huge scope of human genetic polymorphism, harboring about 11 million single-nucleotide polymorphisms (SNPs). Parallel to this, important achievements were made in our understanding that there are genes not only predisposing to a disease development but also to a disease cure. It has been found that the effect of medicines may depend on genotype, both in terms of threshold and magnitude. This new knowledge offers a unique potential for improving healthcare, by improving both drug safety and efficacy, thereby reducing hospitalizations and morbidity related to adverse drug reactions and to ineffective pharmacotherapy. These hopes are accompanied with justified worries about the capacity of the modern state to maintain equity in healthcare to its citizens – including those whose genes might suggest, according to some not-too-distant future scenarios, that certain medicines would not suit them.[9,10] Among the problems such scenarios introduce, as discussed during the workshop panel discussion, the most crucial is 'How can society ensure continued equality in healthcare, along with individualization of pharmacotherapy?'

One of our key concerns when organizing this workshop was to ensure diversity of opinions, so that there would be a fruitful exchange of ideas rather than merely reports about new findings. This is quite different compared with most workshops taking place each year in human clinical genetics, where most presentations typically concern new scientific discoveries rather than policy views. We therefore invited speakers representing different sectors: academia, the biopharmaceutical industry, and regulatory and advisory bodies. The latter included the Federal Drug Administration (FDA) from the USA (Felix Frueh), and The Israel Academy for Sciences and Humanities (Michel Revel). As for academic speakers, we tried to have representation from various disciplines, including basic genetics, clinical genetics, community and family medicine, bioinformatics, bioethics, social sciences, political sciences, and law. We also made an effort to maintain, as much as was possible with our workshop budget, a balanced geographic representation for the European Union, including new member states. Thus, we had speakers coming from the UK, France, Spain, Italy, The Netherlands, Germany, Denmark, Greece, Estonia, and Lithuania. There was a sizable Israeli representation, as well as few US speakers (see final speakers and program poster on the workshop web site: http://www.functionalgenomics.org.uk/sections/activitites/2005/Livshits/info.htm). We were also very pleased to have on board speakers from our neighbors, the Palestinian Authority and Jordan. The workshop registrants, who came mostly from Israel, also included a broad geographic scope, including poster presenters coming from as far away as Durham, North Carolina, USA; Tomsk, Siberia, Russia; and Madurai, Tamil Nadu, India.

In the background information for this workshop, as posted in early 2005 on the workshop website, we gave some background on personalized medicine as follows:

- 'Genetic information technologies are forecasted to completely revolutionize medicine by the year 2050. Patients will be diagnosed and treated, to a large extent, according to their genetic profiles and blood proteomics information.
- Are we prepared for the novel challenges?
- Are we fully aware of the societal and ethical dilemmas that will come along with the revolution in medicine?

This workshop will present the challenges and constraints, and offer insight into potential solutions'.

During the workshop, we heard some contrasting views, including frank observations that the above background statements were oversimplified, too optimistic, or just 'hype'. We heard clear and calculated views explaining why we should not expect too much from genetic information and information technologies (bioinformatics). The views presented at the workshop are summarized in abstracts, printed as a special issue by the recently launched journal, *Personalized Medicine* (Volume 2, issue 2, 2005) and the full contents of the abstracts issue are freely accessible via the workshop website.

Genes and medicine: can individual and community health coexist?

The first workshop day included 16 invited presentations, focusing on 'Health, Genes and Society' (morning and early afternoon sessions) and continued in the late afternoon with a session on 'Medical Genetics and Pharmacogenetics'. The workshop was opened by a keynote presentation by Leo ten Kate (VU Medical Center, Amsterdam, The Netherlands), who is among the key advocates for community genetics and the editor of the journal by the same name. Community genetics is indeed an interdisciplinary field harnessing genomics tools for benefiting society, such as, improving prenatal genetic screening programs. As presented by our keynote speaker, society must ensure that personalized medicine would follow this path, serving the interests of both the individual and the community.

The first session speakers included Klaus Lindpaintner (Hoffman La-Roche, Switzerland), who presented his views as to how personalized medicine should be promoted. He cautioned the audience not to expect too much from pharmacogenomics, as there are obvious limits to what can be predicted from genes alone, and noted that we still have a lot to learn before we can put personalized medicine to practical use. The opening session included a presentation by Carole Moquin-Pattey from the European Science

Foundation (ESF) about the ESF contribution towards building a public–private platform for clinical research in Europe. Among the other notable presentations on the first day, Tim Spector (University College London, UK) spoke about the use of twins in genetic research and its implications for personalized medicine. He demonstrated that twin studies have been very constructive in clinical genetics, and in the same manner have the potential to provide unique benefits for pharmacogenetics.

Genes and health: setting the clinical priorities

The second workshop day featured 12 invited presentations focusing on the medical genetics and personalized medicine themes. Among the speakers of that day were Andre Uitterlinden (Erasmus Medical Center, Rotterdam, The Netherlands), who spoke about analysis of genetic variation in complex endocrine diseases; David Karasik (Harvard University, MA, USA), who presented the complexities of gene environment interactions, using bone mass as an example; Vangelis Manolopoulos (University of Thrace, Greece), who focused on his experience of integrating pharmacogenetics into the clinic at a large hospital in Greece; Uwe Fuhr (University of Cologne, Germany), who discussed individualization of isoniazid doses based on NAT2 genotype; Julia Kirchheiner (University of Cologne, Germany), who presented her work on using the CYP2C9 polymorphism towards genotype-adjusted drug therapy, and Adrian Llerena (University of Extremadura, Spain), who presented new studies on CYP2D6 genetics in Spanish schizophrenic patients.

The second day concluded with a late afternoon oral poster session, in which students, who received prizes of Euro 300 each, kindly donated by Hoffman La-Roche, presented six of the workshop's 14 posters.

Genes and society: many open questions

On the third day, the workshop was focused on 'Genes and Society'. The sessions included talks from numerous disciplines and backgrounds. The speakers of the third day morning included Felix Frueh (FDA, USA), who presented the FDA vision of incorporating genomics data to the drug review and approval process; Michel Revel (The Weizmann Institute of Science, Israel, and the Israel Academy for Sciences and Humanities), who focused on bioethical aspects of prenatal screening; Jeantine Lunshof (VU Medical Center, Amsterdam, The Netherlands), who discussed the societal dilemmas surrounding personalized medicine and key cost-effectiveness considerations, along the lines of 'how much can we afford?';[10] Norbert Paul (Johannes-Gutenberg University, Germany), who talked about unique aspects of public health genetics in Germany with a retrospective on past eugenics horrors in Nazi Germany; Claus Moldrup (Royal Danish School of Pharmacy, Denmark), who presented on bioethical aspects of pharmacogenomics from the pharmaceutical sciences perspective, with a focus on the need to educate the public not to fear the new technologies; and Julie Friedman (Bristol Meyers Squibb, USA), who talked about the ethical concerns in applying pharmacogenomics during the various stages of the drug development process.

The program on the third day afternoon continued with presentations about the theme of 'Pharmacogenomics and public policy'. These included Vaidutis Kucinskas (Vilnius University, Lithuania), who focused on issues of informed consent in biomedical research; Michael Weingarten (Tel-Aviv University, Israel), who highlighted the view that genomics information should not be treated differently from other high-content medical information; Barbara Prainsack (Vienna University, Austria), who presented her hopes for personalized medicine that should not embrace a conceptual dissonance between individual and common benefit; Inga Peter (Tufts University, USA), who spoke about the novel US societal aspects of personalized medicine; and Carmel Shalev (Tel-Aviv University, Israel), who talked about the human rights perspective on personalized medicine and the acute need to maintain justice towards availability of new medicines for developing nations.

The workshop's concluding session featured a talk by David Goldstein from Duke University, NC, USA on prospects for pharmacogenetics and lessons from anti-epileptic drugs.

The workshop concluded with a Round Table panel discussion. The key questions that were preselected for the discussion included:

- Should we oblige industry to do 'something' for people who do not have the right genotype for their drug? What should this 'something' include?
- Equality in access to new health technologies: who pays for genetic diagnostics?
- In how far will individualized medicine change the interrelation of individual and public health, especially with regard to concepts of health responsibility?
- Where do you draw the line about screening fetuses for genetic traits? Schizophrenia, violence, depression?
- How can society ensure better equality in healthcare, along with individualization of pharmacotherapy?
- Will personalized genetic medicine be driven by the pharmaceutical industry in the future?
- What should our priorities be for incorporating personalized medicine into the clinical setting?

No consensus was reached in these discussions. Opposing views were voiced, including within the panel members and from the audience, and there is certainly room for ongoing discussions that would examine alternative

solutions. Moreover, it seems that there will not be a clear-cut solution, but rather, solutions that keep evolving hand-in-hand with emerging pharmacogenetics knowledge, development of new technologies, and the availability of new diagnostics tests. Notably, the discussion included the age-old dilemma of 'nature or nurture' and the roles of genes and environment in the differing response to drugs among patients. There was agreement among panel participants and the audience, although, that discussion on these key questions must continue, and that being able to formulate these tough questions is an essential key step towards formulating the best answers.

Impact on personalized medicine

Public awareness about the scope of adverse drug reactions and the potential of personalized medicine to minimize them has never been more noticeable: recent reports about drug safety issues and the withdrawal of well-known drugs from the marketplace, most notably Vioxx, illustrate how important public awareness and knowledge in this field has become. These recent reports, along with the increased public awareness of drug safety, provide an unprecedented opportunity to dramatically alter the practice of modern medicine, and provide the much needed integration of personalized (individualized) medicine into clinical practice.

Indeed, The Council for International Organizations of Medical Sciences (CIOMS), a division of the World Health Organization (WHO), has recently released a report on pharmacogenetics, pointing out that pharmacogenetic research deserves support from all concerned, and cautioning not to create unrealistic expectations. The FDA also shows increased interest in the potential of pharmacogenetics for improving healthcare, as evident from their web site: http://www.fda.gov/cder/genomics/default.htm.

When discussing genes and health, it is vital to recall that genes alone cannot explain the entire large individual variation in drug response. Indeed, several speakers, including Rivka Carmi (Ben-Gurion University, Israel), Hermona Soreq (The Hebrew University, Israel), Gideon Rehavi (Tel-Aviv University, Israel), Ada Rosen (Wolfson Medical Center, Israel), and Michael Weingarten (Tel-Aviv University, Israel) focused on various nongenomic aspects of personalized medicine. These presentations and discussions lead to the conclusion that the practice of personalized medicine must include proteomics tools in addition to the genomics tools. This would allow taking into account nongenomic effects on drug pharmacokinetics and pharmacodynamics, such as the patients' age, gender, diet, exposure to pollutants, stress, life style, presence of other diseases, etc.

Pharmacogenetics, the research field underlying personalized medicine, is almost 50 years old. The more recent term *Personalized Medicine,* first mentioned in modern scientific literature in 1999, includes a built-in incoherence: medicine is supposed, by definition, to treat the individual patient. Yet, the practice of most drug companies has always been to make 'one size fits all' drugs as a means to maximize their profits. Hopefully, original research and commentaries, coming from different disciplines and presented during our workshop, would contribute to the ongoing discussions about the need to maintain equity in healthcare along with the incorporation of new genomics and proteomics technologies. In the future, such studies would promote the long-awaited change of making medicine truly custom-made for the individual patient, while serving the needs of communities by improving healthcare for every person. Hopefully, a way would be found to achieve such novel goals while ensuring equity in national healthcare services. This goal is of special meaning for the newly expanded European Union, where the roots of democracy were drawn about 2500 years ago, and where the emphasis on human equity in healthcare and education has traditionally been far better established compared with other parts of the globe, ever since the French revolution. Hence, we found it fitting to have included Europe in our workshop title, not only for reflecting on its generous funding by the European Science Foundation but also to signal the unique role that we hope European science and humanities would take towards ensuring equity in healthcare along with the development of the new genomic technologies for improving the quality of pharmacotherapy.

In summary, we believe that pharmacogenetics will not replace, but enhance, existing good medical practice. A deliberate approach starts with investing more in studies aimed at clarifying relations between genotypes and drug response phenotypes (both safety and efficacy), educating healthcare professionals by illustrating the benefits of pharmacogenomics, and by educating society about the potential benefits for healthcare from the new genomics and proteomics technologies. We feel that the Tel-Aviv workshop on personalized medicine has provided a competent venue for this theme.

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Selected web resources on personalized medicine:

AMA (Genetics) Pharmacogenomics: www.ama-assn.org/ama/pub/category/2306.html
BBC News, September 21, 2005: 'Personalised drugs 'decades away'': news.bbc.co.uk/1/hi/health/4267304.stm
Clinical Trials Genomics at FDA: www.fda.gov/cder/genomics/default.htm
Marshfield Clinic – Personalized Medicine Research Project: www.marshfieldclinic.org/chg/pages/default.aspx?page=chg_pers_med_res_prj
NIGMS – The Promise of Personalized Medicine: www.nigms.nih.gov/personalmed/
NHGRI: Personalized Medicine: www.genome.gov/13514107
Pharmacogenomics: Medicine and the New Genetics: www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml
Pharmacogenomics Factsheet: www.ncbi.nlm.nih.gov/About/primer/pharm.html
PharmGKB: The Pharmacogenetics and Pharmacogenomics Knowledge Base: www.pharmgkb.org
PMC: The Personalized Medicine Coalition: www.personalizedmedicinecoalition.org/index.php.