

Personalized Vaccines and Public Health Genomics: Anticipating and Monitoring the ELSIs

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1. INTRODUCTION

A new era of research into strategies for the development and delivery of effective and safe vaccines is now upon us. Against the background of understanding human and pathogen genomic variation, both the fields of bioinformatics and genomics have provided scientists the tools to rapidly screen and identify new candidate antigens for vaccine development. Use of recombinant DNA technology has allowed for the creation of novel DNA vaccines, as well as novel vaccine production and delivery systems, including plant-based and mucosal-based immunization strategies [1]. In parallel, we have seen the emergence of the new field of public health genomics. The latter is a multidisciplinary field concerned with the effective and responsible applications of genome-based knowledge and technologies to improve population health, a definition that resulted from an international meeting held in Bellagio, Italy in 2005 [2, 3]. These developments, combined with the results of the large population genomics projects (e.g., the Human Genome Project, the International Hap Map Consortium and the 1000 Genomes Project) and our improved understanding of genetic differences underlying the individual immune response, have paved the way for the development of efficacious and safe vaccines on a personalized or sub-population level based on genetic differences. This emerging intersection of vaccinology and population based genomic sciences has been termed “vaccinomics” [4, 5] or “personalized vaccines” and is thought to have the potential for impacting the clinical outcomes with relevance for public health, including maximizing immunogenicity and minimizing the risk of vaccine complications or failure.

Similar to small molecule pharmaceuticals, there are marked person-to-person and population differences in vaccine safety and efficacy. Much like pharmacogenomics is based on the premise that information concerning genetic differences at the individual and population levels can be used to develop safe and effective pharmacological treatments aimed at sub-groups in the population, the development of personalized vaccines is based on the premise that variations in genes regulating the host immune response can be exploited to develop safer and more effective personalized vaccine strategies. For example, genes of the

human leukocyte antigen (HLA) system are among the most polymorphic genes in the human genome and play a major role in regulating immune response to vaccines and infectious agents [6, 7]. Indeed, polymorphic differences in HLA genes have been associated with development of cervical cancer, as well as immune response following hepatitis B and measles, mumps, rubella (MMR) vaccines [4]. Population based genetic differences are also thought to contribute to rare vaccine related complications, while gender based differences have been observed in the immune response to some vaccines such as smallpox [4]. By exploiting this knowledge in the postgenomics era, “personalized vaccines” have tremendous potential for improving public health and preventing the spread of threatening and emerging infectious diseases by enabling clinicians to deliver the right amount of vaccine to the right person at the right time. There is also a possibility in the future that chronic conditions, such as cardiovascular diseases and cancer, commonly considered beyond the scope of vaccination, could be targeted [1].

While vaccination is considered to be one of the greatest accomplishments of public health and one of the most promising health initiatives to improve health in developing countries, “personalizing” the most collective of public health tools will have a profound impact on vaccine development and public perception and participation. Scientific enquiry related to personalized vaccines has rapidly emerged and is growing into its own discipline; however, little discussion of the ethical, legal, and social issues (ELSI) specific to this area has occurred. Thus, the need exists to expand the debate to include socio-ethical reflection on research practices and clinical applications in this field. The goal is not to paint an unnecessarily alarmist portrayal of the much anticipated personalized vaccines, but rather to ensure that researchers and policymakers in this field are aware of not only the scientific, but also the socio-ethical ramifications of their work. Indeed, scientists, policymakers and ethicists need to take the time to reflect on the social, ethical and legal ramifications of personalized vaccines in order to take the appropriate steps to ensure optimal integration of this new genomics application into public health. To this end, we wish to emphasize that public health genomics can prove to be a very appropriate and timely lens through which personalized vaccine advances can be evaluated and monitored as the field of personalized vaccines progresses. Hence, the current editorial aims to encourage a multidisciplinary debate on the ethics of personalized vaccines by highlighting several broad fields of inquiry that warrant further investigation. To our knowledge, it is the

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first attempt to address the ELSIs of personalized vaccines in the literature.

2. PERSONALIZED VACCINES

2.1. Lessons From Pharmacogenomics and Past Genomics Applications

Genetics and genomics have generated a vast corpus of ethical reflection in the last thirty years. Indeed, some would even argue that genetics has attracted a disproportionate amount of attention from ethicists and policymakers compared to other branches of health research. Rather than initiating ethical reflection *ab initio* on personalized vaccines, it seems reasonable to examine whether the recent work undertaken in the context of genomic research could be relevant to the field. As previously seen, one realm of genomic research that appears to have a particularly close relationship with personalized vaccines is that of pharmacogenomics in the context of “targeted health interventions”, a subject of prime importance for the CPPM readership and the global personalized medicine community. These two disciplines share a common interest in kinetics (e.g., time course of drugs or vaccines) and dynamics (e.g., the biological effects of drugs or vaccines on the host organism), risk-benefit assessment and adverse events [1]. Moreover, as the development of drugs and vaccines are both cost and labor intensive in both disciplines, public-private partnerships will be necessary for research findings to be translated into tangible clinical applications.

Generic ethical issues (i.e., issues shared with other types of genomics research) include the following:

- database issues (confidentiality, intellectual property, ownership, and interoperability),
- disclosure of results,
- informed consent (allowable scope of consent and withdrawal of consent) and,
- discrimination/stigmatization, among other previously familiar topics in the context of genomics ELSIs.

Conceivably, it is likely that these generic ELSIs will manifest themselves in some form or other in the context of personalized vaccines as well. Researchers engaged in personalized vaccine development would do well to keep informed of the ELSIs and attendant policy measures governing genetic/genomic research to have a better handle on these issues prior to starting their own projects.

Other ELSIs, more specific to the context of pharmacogenomics research have also been identified. These issues result from the particularities of the health intervention (e.g., drugs, vaccines) development process (i.e., clinical trials) and the close link that exists between academic genomics researchers and industry. This second group of ethical issues include: impact of genotyping on the clinical trial process, conflict of interests, commercialization of academic research, need for increased impartiality in the reporting of research findings, priority setting (which disease to address? / which population group to target?), “ethnic drugs”, orphan groups, and informed consent in add-on genomic studies. In reference to these ELSIs, there is

currently a scarcity of policies specifically addressing the field of personalized vaccine development. Hopefully, the applications of genomics to targeted, subpopulation based vaccine development will provide an even greater incentive for researchers and policymakers to proactively reflect on the ELSIs emergent from the past genomics research in the newer context of vaccinology and public health genomics. To this end, it is reasonable to suggest that personalized vaccines will form yet another subspecialty of public health genomics. Study of ELSIs in this field will warrant an approach that is both anticipatory and makes use of empirical (quantitative/ evidence based) field work. Some of the conceivable ELSIs unique to this field are discussed in the next section.

2.2. Personalized Vaccines and “Novel” ELSIs

A third set of ELSIs also found in the context of personalized vaccine research is particularly preoccupying. While some can already be anticipated, others are likely to be discovered through more in-depth investigation or arise as research in this discipline progresses. To this end, it is notable that vaccinomics research aims to foster the development of “personalized vaccines”. More accurately, it proposes to move from universal vaccines to vaccines that will target smaller well-defined population groups (e.g., based on human genomics variation, geographical origin, sex, age, etc.) [8]. Given that vaccination has a fundamental public health objective where success is dependent on achieving herd immunity, one could question whether this novel subpopulation based approach will be efficient to counter global public health threats. At first glance, it would seem that while a personalized vaccine strategy may not be ideally suited for rapidly emerging and highly contagious diseases such as influenza virus, personalized vaccines may represent a promising strategy for less contagious diseases, or chronic health conditions, such as cancer or diabetes. More research, however, is needed to examine this hypothesis in more detail. Moreover, the question can be asked as to whether a small group of individuals with a rare genotype, or a group in a developing country could be neglected by personalized vaccine researchers and companies interested in vaccine development. Although the issue of orphan groups has been raised in the context of pharmacogenomics [8], the negative consequence of being a “vaccine orphan” would be indeed much more serious. Here, the therapeutic potential, and the potential adverse effects of vaccines are likely to be considerably more important than those of regular medicines.

While the theoretic potential for personalized vaccines appears promising, in practice economic and practical considerations may limit its use as a public health tool. For example, it may not be practical for health authorities to suggest/require genotyping on an entire population to prevent undesirable effects for a small minority of individuals. Genomic stratification may complicate and lengthen the vaccine development process. But, with globalization, we are facing an increasing number of pandemics that develop at an even faster pace than ever before. Thus the question: are personalized vaccines relevant to the current international public health context?

Other economic and social considerations emerge in the context of developing countries, where personalized vaccines holds great potential to address public health issues unique to these regions. In fact, recombinant technologies to develop vaccines against infectious disease have been rated as one of the most important biotechnologies to improve health in developing countries [9]. However, considering the cost implications of personalized vaccine development and the profit oriented interests of the private sector, it remains to be seen whether the development of personalized vaccines will decrease or increase health disparities between developed and developing countries. Stringent use of intellectual property rights over new personalized vaccines or tests could have a very detrimental impact on uptake in developing countries. It would be unfair if early personalized vaccine studies for adverse reactions were performed in developing countries, for vaccines that would eventually be available (or relevant) only for populations in the northern hemisphere. The recent efforts of the pharmaceutical sector to facilitate access to drugs in the developing world [10] and the growing number of public-private partnerships allow us to remain cautiously optimistic about the potential of personalized vaccines for developing countries. Nevertheless, production and access costs of genomics personalized vaccines should be carefully monitored by policymakers in the interest of public health and global equity.

Finally, socio-ethical issues may also play a significant role in any eventual uptake of a personalized vaccines strategy in society. Vaccination campaigns are not always well-received by the population; recently they have been met with a degree of suspicion by stakeholders. The recent controversy over the fast-tracking and marketing of the HPV vaccines [11], as well as the weak compliance with the H1N1 vaccination campaigns in some countries [12, 13], illustrate this phenomenon well. The introduction of genomics, which itself has also generated a fair amount of trepidation over the years into the equation, could have the untoward effect of increasing the strength of the existing anti-vaccine movement. To avoid such potential outcomes, researchers and pharmaceutical companies will need to place increased emphasis on transparency, public information, conflict of interests avoidance and accountability.

3. CONCLUSIONS

Personalized vaccines have the potential to be one of the most promising genomics applications in public health. Personalized vaccines could improve global health by addressing some of the most threatening diseases of our time. In order to ensure that personalized vaccine research and development are not derailed by unforeseen novel ELSIs, it is important to think ahead about the potential pitfalls and socio-ethical repercussions of research in this field. We hope that stakeholders will draw on the genetics/genomics research ethics experience gathered within the last

thirty years in order to develop ethical and policy frameworks that will facilitate the efficient, equitable and ethical development of personalized vaccines for the greater global good.

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DUALITY/CONFLICT OF INTERESTS

None declared/applicable.

ABBREVIATIONS

DNA	=	Deoxyribonucleic acid
ELSI	=	Ethical, legal and social issues
H1N1	=	Influenza A virus
HLA	=	Human Leukocyte Antigen
HPV	=	Human Papillomavirus
MMR	=	Measles, Mumps, Rubella

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