Whole genome sequencing followed by preimplantation genetic diagnosis.
A translational approach to ethical issues

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Abstract

Translational research is a recent concept, whose main aim is to categorize practical, outcome-oriented research. Preimplantation genetic diagnosis (PGD) is a diagnostic method used to determine the human genotype before implantation through artificial insemination. This method is very useful in identifying possible genetic syndromes in fetuses whose parents have a high risk for genetic diseases. There are numerous techniques for performing PGD, like quantitative polymerase chain reaction or array technologies (comparative genomic hybridization arrays or karyomapping), already used for detecting aneuploidy, unbalanced products of parental chromosome rearrangements, deletion or duplication of genetic materials, and so on. Whole genome sequencing could be used in the next years for PGD, as the technique has already become cost-efficient. However, the use of these techniques in clinical practice may pose a series of significant ethical issues. This article we will try to summarize a few ethical issues associated with whole genome sequencing associated with PGD, including positive eugenics, transfer of knowledge, teleology of the newborn baby or commercialization.
Keywords: *whole genome sequencing, preimplantation genetic diagnosis, ethics, translational bioethics, positive eugenics*

Introduction

Translational research is a recent concept, whose main aim is to categorize practical, outcome-oriented research[1]. In medicine, it appeared quite recently, and it has a still fluctuating definition, especially regarding the number of phases and other elements of the process[1-5].

Most current definitions considers it as a process that begins with fundamental research (genetics, molecular biology, proteomics, and so on), and ends at a worldwide level (social healthcare, access to healthcare or education)[6]. Reproductive ethics is one of the most studied subfields of bioethics, starting with its history toward new trends like cloning, genetic engineering, production of designer babies, post-humous sperm procurement associated with *in vitro* fertilization, and so on[7-12].

Preimplantation genetic diagnosis (PGD) is a diagnostic method used to determine the human genotype before implantation through artificial insemination[13,14]. This method is very important in identifying possible genetic syndromes in fetuses from parents with high risk for genetic diseases.

Nowadays, PGD is widely used in many centers worldwide to identify possible diseases before *in vitro* fertilization.

The procedure consists in performing biopsies of multiple embryos created by *in vitro* fertilization and screening for aneuploidy or single-gene mutations, and then selective implantation of the embryos[15]. There are numerous techniques for performing PGD, of which the most recent routinely used nowadays in clinical practice are quantitative polymerase chain reaction or array technologies (comparative genomic hybridization arrays or karyomapping), already used for detecting aneuploidy, unbalanced products of parental chromosome rearrangements, deletion or duplication of genetic materials, and so on.

Whole genome sequencing (WGS) is expected to be used in the next years for PGD, as the technique has already became cost-efficient[16]. These techniques could allow, amongst other, detection of carrier status for numerous genetic defects, risk factors for multifactorial, adult onset diseases like heart diseases or diabetes, or identification of recessive disorders.

The translational process of translating WGS data to PGD and further can be synthesized as in Figure 1.

However, the use of these techniques in clinical practice may pose a series of significant ethical issues. In the following phrases we will try to summarize a few ethical issues regarding the association of WGS with PGD.

Eugenics

Nowadays, PGD is mainly used (i.e. legally) by parents who have a history of genetic diseases, or who had a child with a genetic disease, and want to have
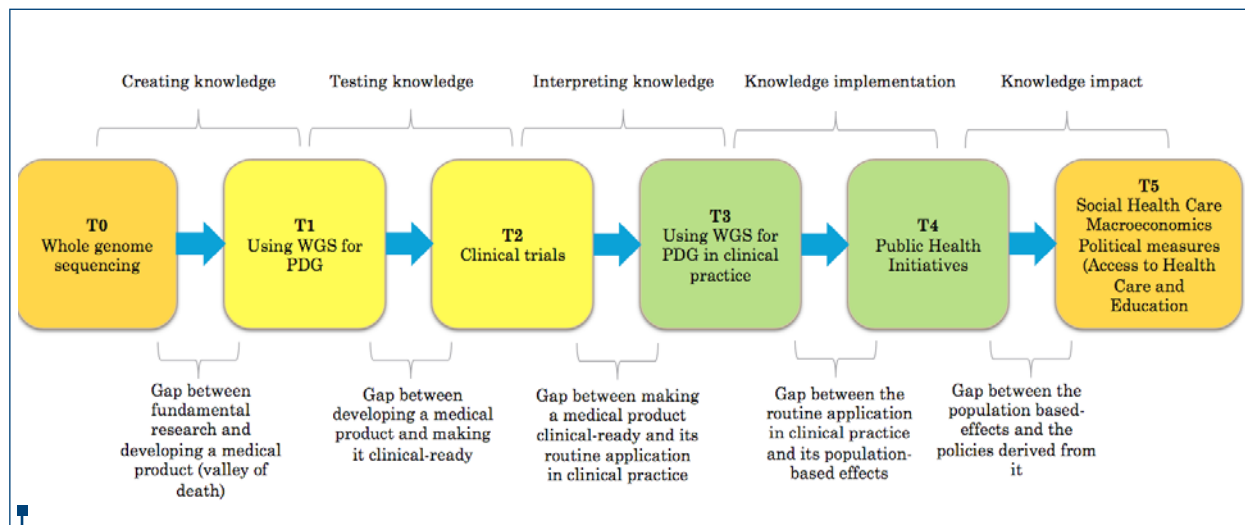
Figure 1. *The translational process of translating WGS*

another child without it. WGS can increase significantly the potential uses of this technique from detecting and maybe even correcting mutations associated with various risk factors for genetic or multifactorial diseases, to selection of embryos with certain desirable characteristics. Moreover, WGS can be used conjointly with other genetic engineering techniques, leading the way to creating truly designer babies. These additional uses can be easily considered as positive eugenics, leading to the selection of individuals with a favored set of desired characteristics, which in itself cannot be considered prima facie bad. Who wouldn't like to have tall, beautiful, disease free children?

However, this outcome is only one facet of the issue. WGS, followed by PGD is, even if the cost for WGS decreased significantly in the last years, an expensive procedure, whose costs must be paid by somebody. If the procedure is paid by the state, only developed countries could support such a burden, increasing the gradient of disparity between richer and poorer countries. If the parents pay the procedure, again it would cause an increased gradient of disparity between healthier and poorer parents. Both could lead to the appearance, in a short period of time, of two distinct classes - one with people having fewer (if any) genetic defects, better looking, more intelligent, stronger, with an increased capacity to adapt to the environment, and one with "regular people", without any genetic advantage.

The appearance of such disparities would be contrary to one of the fundamental principles of bioethics - justice, as by using medical techniques we would basically create two casts of people with unequal chances of being successful in their social and economical environments.

Another major issue is represented by the uncertainties about the effects of a certain genetic manipulation or the selection of a certain desirable genetic phenotype. The product of a certain gene can alter more than one metabolic pathway. Maybe an allele decreasing the risk for primary hypertension might unknowingly increase the risk of schizophrenia.

Therefore, a mass selection of that allele, even if it would decrease slightly the risk of arterial hypertension, could lead in time to a significantly higher number of schizophrenic persons.

Many authors consider that this risk could be minimized by the non-directive principle of genetic counseling, which states that the physician should present the options to the patients completely unbiased. The patients would have all the facts, and would decide whether, and which characteristics should be desirable, and should be selected in the embryos that would be implanted. Therefore physicians will not do any type of positive eugenics.

In practice however, the non-directive principle is often overlooked, especially by physicians from countries other than Western Europe and US. For example Wertz and Fletcher, while performing a survey on almost 3000 genetic counselors and geneticists from 37 countries, when asking whether "an important goal of genetic counseling is to reduce the number of deleterious genes in the population" received a positive answer from 13% of UK geneticists, around 50% from geneticists working in Eastern and Southern Europe and almost 100% from geneticists working in China and India[17].

Transfer of knowledge

In order for physicians using PGD to use information from WGS techniques, they should properly understand it and apply it in clinical practice. However, genetics is not a fundamental part from the Obstetrics & Gynecology curriculum, allowing sometimes misunderstandings to appear in the transfer of information from Phase 0 to Phase 1.

Relevant information about some genetic data might be missed out by researchers performing studies on Phases 2 or even later on, potentially leading to an increased

risk for the appearance of unforeseen effects of certain genetic data manipulation, that could potentially be caught only on large scale studies, or even more severe, after more than one generation of persons born with these techniques. Therefore these kinds of techniques should only be used scarcely, in instances where the benefit is obvious (identification of major genetic defects), and not to be left to handle all potential risk factors for chronic diseases or selection of desirable traits[17].

End in itself and teleology

According to the Kantian philosophy, every human must be an end in itself, and not only a means toward reaching a certain end. By selecting disease free babies, with maximum strength, beauty, or intelligence, parents are actually transposing their wishes and desires upon the children. This "superior" genetic pool should theoretically allow the maximization of the chances of the children to survive, and reach happiness. However we are not only genes, our development being influenced by the environment, social interactions, culture, and so on. By diminishing the gene pool of our offsprings, a direct consequence of WGS followed by PGD, we will only predetermine their life, and decrease the diversity that actually caused us as a species to evolve to what we currently are, but also the possibilities that we have to respond to the environment. Moreover, our offsprings will not have the free to choose their path in life. If the parents have chosen an embryo with a genetic pool assumed to give high intelligence, there are smaller changes that the child will be an artist, or a fisher, or maybe even an empathic or a good person[17,18].

Commercialization of the human product

Nowadays most babies are born naturally, and their genetic pool is strictly randomized. No one knows whether the child will have blue eyes, or high intelligence, or a perfect body.

By allowing selection on various criteria of the embryos to be implanted, more and more persons that will have the finances to do so will chose this method, based on their natural wish to maximize the benefit of the children.

However, this will lead to an increased rate of commercialization of the human product - medical centers will promote themselves as being the ones who will be able to select a maximum number of desirable traits, *in vitro* fertilization will be used as an alterative method by more and more fertile couples just for the sake of this technique, an increased number of viable embryos will be discarded, and so on.

We will be with a step closer from designer babies[18], and we will not be able to stop this phenomenon.

Conclusions

Even if we only summarized a few main ideas regarding ethical issues determined by WGS followed by PGD, it is clearly visible that such a technique should only be used if all potential risks of the various genetic engineering techniques and all potential interactions are fully understood.

Moreover, due to the potential eugenics and discrimination risks, its use should be clearly regulated, with well-defined norms detailing each potential application/ selection of specific genetic profiles. ■

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