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Statement of the board of the Society for Medical Genetics CMA JEP on premature commercialisation of predictive genetic screening in common diseases, i.e. the issue of so-called "genetic horoscopes"

Due to the rapid development of predictive genetic screening (PGS) in the Czech Republic and in compliance with recommendations of the European Society of Human Genetics, American Society of Human Genetics and the "Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Genetic Testing for Health Purposes" issued by the European Council (see literature), the Society for Medical Genetics CMA JEP (www.slg.cz) issues an expert statement warning against premature commercialisation of such genetic testing.

The present discussion on PGS for common adult multifactorial diseases is most welcomed by SMG. According to definition, PGS means systematic, active offer of genetic screening for a wide range of genetic alterations associated to various degree with the development of certain common diseases made to specific cohorts within a population (such as women, children). The test results, however, present only clinically negligible modification of risks (in the positive or negative sense) posed by the tested diseases disregarding other, more consequential extraneous factors, such as lifestyle, smoking, etc.

The only advantage of PGS when offered to healthy citizens is that, as a result of the procedure, they may realize what importance genetic factors have for their future. Unfortunately, the advertised screening is not targeted and so it represents only a blanket screening for various mutations or variations (hereinafter only alterations) within the human genome that, based on previous epidemiological studies (often made on populations rather removed from ours and so genetically irrelevant!), were to varying degree associated with the development of specific diseases.

Despite the fact that SMG respects clients' or patients' autonomy in deciding on obtaining information concerning their genetic profile, we are obliged to guarantee *lege artis* medical genetics methods and warn the clients / patients / indicating physicians of serious problems related to such genetic testing.

The clinical impact of the tested alterations is only minimal

The practical clinical impact of alterations currently tested by PGS is only negligible, as they can increase the health risks only in the order of few per cents at most. Human genome sequencing performed lately on larger numbers of people has shown that various genomic alterations are often found also in healthy adults and their detection thus cannot be "automatically" interpreted as positive or negative with respect to the specific health risks. This can lead to unnecessary iatrogeny or "false reassurance" in the patients concerning their lifelong "health prognosis".

Currently available methods do not allow for correct evaluation of interactions between the alterations tested

Reliable evaluation of complex interaction between the alterations detected is also unavailable, including their variable expressivity (i.e. the extent of their clinical impact) or

penetrance (i.e. whether they manifest at all). The latest researches have shown that increased amount of alterations tested does not raise the "degree of predictivity" for the disease. For instance, if there are three alterations of protective nature and then more associated alterations are added, the risks may divert in the opposite direction. Similar "risk oscillation" occurs also when the number of alterations is further augmented. Moreover, the highly complex field of "genomic interactions" has not been reliably explored yet. It seems that with respect to the radical impact presented by lifestyle and adherence to existing therapy, where the resulting effect shows in the order of tens of per cents (!), including standard preventive recommendations from general practitioners, the genetic factors in multifactorial diseases are only of minimal consequence.

The present methods of health care education, prevention and therapy are currently unable to make use of the commercial predictive screening

Our health care system has sufficient educational mechanisms available provided by general practitioners and media, while PGS, as currently performed, shows no practical assets nor does it lead to treatment optimization. Untargeted search for genetic alterations omitting complex examination of the patient and lacking the knowledge of the overall context, personal and family medical history etc. is, from the clinical perspective, premature and represents a *non-lege artis* method (see literature).

PGS has been as yet carried out outside the scope of the standard health care system, where molecular genetic screening is usually recommended for patients who have undergone proper genetic counselling by medical geneticists provided in conjunctions with the specialists referring the patient for targeted investigation of medically serious genetic risks. This standard procedure also complies with domestic and international expert recommendations (see literature).

Our statement is not a matter of "competitive fight or disguised commercial interests"

SMG should also emphasize that we have not been prodded to this statement by any commercial or competitive interests but by the above expert positions. PGS technology is generally available, although we do not make use of it for the above stated reasons. It is not a coincidence that "genetic horoscopes" are often mentioned in international scholarly literature in connection with PGS.

The role of general practitioners in indicating the predictive screening

SMG appreciates greatly the existing good cooperation with general practitioners and deems it highly important that the colleagues were informed of the PGS limitations and of the necessity to responsibly consider, whether it is more suitable to recommend PGS or indicate standard genetic counselling to a patient that will lead to targeted and *lege artis* performed molecular genetic screening. Experience from abroad has shown that patients often make the decision on whether or not to have PGS done in view of their loyalty to the general practitioner. We would therefore like to take the liberty to appeal also to generally accepted ethical aspects of medical practice!

International scholarly activities reflected by our statement

For the above reasons and due to uncontrolled spread of PGS offered by private entities, international and domestic scholarly societies have issued a series of warning statements (see literature). Legislative measures are currently undergoing approval in Germany aimed at restricting *non-lege artis* methods employed in genetic testing (Gen-Gesetz).

Also our scholarly society reacts to this worldwide trend and submits to health insurance companies and governmental authorities the below stated recommendations. In addition, this statement should serve as a guideline for including or excluding certain forms of genetic testing into or out of the public health insurance system.

SMG's recommendations concerning PGS as currently performed

1. SMG recommends that testing of high risk genes (serious mutations on highly "penetrant" genes, such as *BRCA1/BRCA2* breast cancer genes) were performed only by specialized medical genetics centres. The laboratories listed in CZDDNAL UHKT Praha database (http://www.uhkt.cz/nrl/db) are subject to domestic as well as international quality assurance control and the examination as such is carried out according to internationally recommended procedures. The potentiality of incorrect results is thus reduced to minimum and the appropriate genetic counselling as well as consequent medical care are ensured.

2. Testing for limited number of mutations in high risk genes during PGS is clinically disputable, since in majority of syndromes (e.g. tumour syndromes) each family may carry its own individual mutation. Negative result obtained from such limited testing provides only minimal clinical asset and may result in risk underestimation and restriction of regular standard prevention, such as mammography. Insufficient population "capture rate" in this field is, in addition, unethical and the tests are in contradiction with all international expert recommendations!

3. To this end, SMG recommends that all families with suspected hereditary tumour syndrome were referred for testing to clinical genetic centres where the entire risk genes are examined in full. In the Czech Republic, genetic testing for medical purposes must comply with qualitative requirements based on internationally adopted recommendations (see literature). It is essential that the test results (positive as well as negative ones) were interpreted correctly by a clinical geneticist who, in conjunction with a specialist, should be able to properly assess the degree of individual risk.

4. PGS for alterations in low risk genes as means to modify "predictive risks" in common adult multifactorial diseases has not been yet recommended for clinical use by all scholarly societies. Result interpretation is disputable, often leads to incorrect prognoses and may be even harmful to the patients. Epidemiologic study results serving as the source of information for PGS are not meant for clinical use as of yet.

5. In their unsubstantiated advertisement for PGS, commercial entities overestimate the positives and insufficiently account for substantial limitations posed to the client / patient and, in particular, for the negligible impact PGS results have in the clinical practice of the indicating general practitioner (see above). PGS advocates overrate the right "to know" against the equally important right "not to know", especially in cases where targeted prevention or therapy is unavailable for the disease the patient / client is at higher risk for as indicated by the PGS results.

6. Entities offering PGS do not operate in compliance with standard principles of genetic testing. The "services" offered are not transparent – no exact listing of the tested genetic alterations is disclosed as it is considered a "trade secret"! Moreover, the "offer" frequently changes in time rating the process as outside the scope of standard health care system which requires that the clinical effectiveness of any examination be assessed.

7. SMG is also bound to point out material violation of all international recommendations in cases where PGS is offered to minors. Predictive risk testing in children under 18 years of age is strictly defined by an indication spectrum as it is related to a whole array of ethical issues (see literature). SMG therefore strictly opposes any PGS of minors!

8. Under certain circumstances, predictive testing results may become discriminating. Access to commercial insurance or even health insurance could be prevented or altered due to "increased" genetic predisposition. SMG consequently disproves of PGS in instances where the data could be used for unequal access to or even revision of health insurance based on "false positive" genetic predisposition. In compliance with all international biomedical conventions and expert recommendations, SMG also disproves of PGS performed in the course of any hiring procedure.

Conclusion

In the long-term perspective, the scientific progress in applied genomics is headed towards personalised medicine and it is to be assumed that in the future such information could be used in clinical practice. Nevertheless, the clinical use of results gained from top genomic research as offered by PGS is at present premature and may even be harmful to patients!

Advocates of commercial PGS such as "DTC – "Direct to Consumer" (see literature) state that majority of the genetic tests performed in the course of predictive screening for multifactorial diseases is not meant for clinical purposes but is of "educative nature". They, therefore, believe that the companies need not comply with requirements stipulated by "Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Genetic Testing for Health Purposes" or „OECD Guidelines for Quality Assurance in Molecular Genetic Testing" (see appendices).

Similarly, according to PGS advocates, the companies are exempted from the domain of international expert recommendations because they operate outside the standard health care system. Despite that, the entities offering PGS often combine "educative testing" of low risk genes with high risk genetic factor testing such as limited spectrum of alterations associated with the hereditary variants of breast cancer and so on. This "brings them back" to the standard health care system rendering them clearly subject to such requirements! The offer of such "cocktails of genetic alterations presenting varying degree of risks" exposes the indicating physicians to ethical as well as practical dangers of *non-lege artis* methods. Moreover, the risk of underestimating regular oncologic prevention is substantially increased in patients with "false negative" results obtained by using insufficient number of population specific alterations in the highly penetrant genes.

And finally, it should be realized that as a part of long-term prospective observation, PGS may be able to provide the required data on potential relevance between genomic alterations and the actual risks posed by the disease. Such process should, however, be transparent and subject to the same qualitative requirements as any other medical research.

For the indicating general practitioner it is very difficult to decide what genetic factors are clinically relevant and/or how reliable the PGS results are. It is, therefore, important to discriminate between the actual medically indicated, *lege artis*, targeted genetic screening and the "recreational" (or "educative") PGS, representing above all the individual interest of the client in his or her genetic profile, that is excluded from the set of examinations indicated within the standard health care system.

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