

MUSINGS

'Genomic counseling'? Genetic counseling in the genomic era

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Genetic counseling can be seen as the health professional role concerned with the impact of genetic disease and genetic information on individuals and families. It has been predominantly concerned with the human problems arising in the context of single gene disorders, chromosome rearrangements and malformation, including syndromes of neurodevelopmental disturbance and dysmorphic physical features. These are the core conditions dealt with in genetic counseling practice on both sides of the North Atlantic, although the scope of genetic counseling does vary between countries so that, for example, North American genetic counselors are often heavily engaged in the offer of routine antenatal screening to pregnant women, whereas this is not standard practice in Europe. As genomic analysis enters clinical medicine [1,2], it is timely to reflect on the impact that this will have on genetic counseling practice [3]. Instead of merely single gene test results, will genetic counselors undertake risk counseling for the common, complex disorders on the basis of pan-genome test results such as genome-wide single nucleotide polymorphism (SNP) panels, array comparative genome hybridization studies of copy number variants, exome sequencing or full genome sequence? If they do, what impact will this have on the prevention and treatment of the chronic diseases that seem likely to be the major health problems of the 21st century?

For now, no reputable professional - genetic counselor or other clinician - is using SNP array results in relation to complex diseases as the basis of health care interventions or to support recommendations about lifestyle: the validity of such interpretations is insufficiently robust and there has been no demonstration of clinical utility [4,5]. However, once genome sequencing is widely available and readily affordable, many of the obstacles to the demonstration of validity will (eventually) disappear,

although it will take time for the clinical research community to develop confidence in the interpretation of the accumulating data. At that point, whenever that comes to pass, will genetic counselors embrace the genomics of complex disease as well as the genetics of Mendelian disease?

Our answer is a Yes and a No and a Maybe.

Yes

The principal clinical application of genome sequencing has so far been the recognition of 'new' Mendelian loci responsible either for previously unrecognized disorders or for additional loci contributing to known clinical entities. As the cost of genome sequencing approaches the cost of mutation searching in multiple loci associated with a disease presentation, such as hypertrophic cardiomyopathy or retinitis pigmentosa, genome sequencing will be performed because it will be a cheaper means to resolve the locus heterogeneity or to distinguish the unusual Mendelian forms of a common disease from the much more frequent sporadic cases. The clinical application will be driven by a Mendelian logic: even conservative and cautious genetic counselors will use such information gratefully as it will allow them to give useful answers to their patients and their patients' relatives more frequently and more rapidly.

There will, however, be a less clearly useful - and less welcome - spate of information to flow from the genome sequencers. Alongside the information that is actively sought and desired because it is of practical relevance, there will be information of uncertain significance. First, there will be nonsense and frameshift mutations in the coding regions of 'important' loci previously associated with a disease phenotype. There will also be information about the less common copy number variants (CNVs), whose significance may depend on gene-by-gene interactions, such as those applicable in development that led to the 'two hit' model of developmental disruption. There will be SNP data of possible but dubious relevance to the common complex disorders, and data about variation able to modify the phenotype of 'Mendelian' disorders. There will inevitably also be other, emergent findings and applications of such data.

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It is going to take years for us to interpret such variants with confidence. The question will be raised as to whether 'difficult to interpret' information should be released at all or only the information specifically sought. We do not think that restricting the release of information about sequence variants will be a sustainable position - and it may be unhelpful in retarding the development of our collective genome-interpreting skills - but in the short term it may be an attractive transitional strategy.

Our 'Yes,' therefore, is a recognition that genetic counselors will have to deal with the interpretation of genomic information relating to the risk of the common complex diseases simply because the information will be there and it would be unreasonable to ignore it. So our Yes is uttered in a somewhat reluctant, resigned voice. Much of this will be a distraction from the real work of answering the questions that counselors have been asked and giving the information in which they have real confidence.

No

But will genetic counselors engage with genomic information relating to complex diseases with the goal of interpreting it for the '(wo)man in the street,' in the absence of a relevant family history and simply as a basis for making lifestyle and health screening decisions? Here, we think the answer will be No - for several reasons. First, whereas genetic counselors are well trained to help individuals and families tackle decisions about predictive testing, prenatal testing and family communication in the face of large (Mendelian) risks, their skills will not be so relevant when families confront complex genomic information, for which 'predictive' testing is not available and when the applicability of the information for reproductive decisions and family communication is small. However, although they might be clinically trivial, the role that perceived genetic risk could have in adherence to prevention and treatment has the potential to be important and is currently not well understood. There is a commonly held clinical view that information about 'genetic risk' has the potential to improve compliance but, in fact, there is evidence that understanding a risk to have a genetic etiology has little or no impact on adherence to preventative and treatment strategies [6].

However, this territory - decisions about lifestyle and about appropriate participation in population screening programs - is that of primary health care professionals, who are established on a scale appropriate to the challenge, whereas genetic counselors are far too few. It seems unlikely that it will be very useful in the short term to apply genomic investigations to risk prediction for coronary artery disease [7] and other vascular disorders at the population level; this adds little to the predictions of disease risk from simple endophenotypes, such as

blood pressure, serum cholesterol and the body mass index. Genetic counselors, however, do have an important role in educating primary health care practitioners and advising on appropriate criteria for referral of families to genetic services.

Finally, genetic counselors may choose not to become engaged in 'genomic health risk' assessments, in that the style of support they usually provide in making decisions differs fundamentally from that appropriate here. Genetic counselors usually help clients to weigh up the personal and family consequences of particular decisions, whereas 'genomic health risk assessments' will have to focus their attention much more on promoting or achieving the desired behavioral changes. The genomic health risk assessment may indicate specific personal targets for the intake of certain foods - especially vitamins or other micronutrients - but for most people the recommended diets and lifestyles will be much the same even if the strength of the evidence underlying the lifestyle prescription may differ in detail between individuals. It seems from the limited evidence available that the endorsement of lifestyle advice by gene-based analyses gives recommendations about lifestyle little additional weight [8] and may raise troublesome processes of adjustment [9]. That leads to the question of whether the accumulation of genetic and clinical data in gene databanks will prove helpful in permitting the dissection of behavioral propensity to exacerbate risk from the underlying physiological or metabolic predisposition to the disease. Will it prove helpful - even if it is possible - to tease apart these entangled and interacting variables?

Maybe...

We are tempted to imagine that discrimination between the genetic basis of a behavioral propensity and a physiological predisposition to disease will have little clinical application, particularly while behavioral adaptation remains the best preventative strategy. If a person is predisposed to disease, at least in part because of a predisposition to behave in an 'unhealthy' manner, then there is great potential for awareness of the behavioral propensity to interact with the propensity itself in making future decisions. How this interaction will play out is unknown but, given the well established role of self efficacy in successful behavioral change, it could easily undermine attempts to change [10]. Alternatively, such genetic information might lead to a better understanding of the difficulties an individual is facing and so perhaps to better-tailored intervention strategies. If asked whether such genome-wide information about behavioral propensities will be helpful in practice, alongside information about physiological and metabolic propensities, we answer 'Maybe' because the outcome of such self-aware processes of interaction cannot, even in principle, be

computed. Any attempt to predict the outcome of such interactions across such a diverse range of complex conditions would be unwise and appear naïve.

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