European Journal of Human Genetics (2012) 20, 483–485

www.nature.com/ejhg

NEWS AND COMMENTARIES

Limits of DTC

Direct-to-consumer genetic testing services: what are the medical benefits?

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European Journal of Human Genetics (2012) **20,** 483; doi:10.1038/ejhg.2011.229; published online 4 January 2012

Over the last years, several private companies have developed direct-to-consumer (DTC) genetic testing services that directly propose to consumers genetic tests outside the context of a genetic counseling session (for review see Bloss *et al*[1]). The argument usually presented by these companies is that DTCs facilitate access to testing and increase consumer awareness of the risk of developing diseases. The number of available DTC tests is rapidly increasing with tests for Mendelian disorders resulting from a deleterious mutation to tests for multifactorial diseases, due to a combination of DNA variants. Most of the DTC tests analyze common DNA variants, which are present in the general population and have been shown by genome-wide association studies (GWAS) to be associated with a low or moderate increase of disease risk. Although there is no reason why private companies could not participate in genetic testing, as long as their practice respects the general guidelines in genetics, the development of such DTC genetic testing raises numerous issues. First, DTC is clearly taking advantage of the underestimation by the consumers of the complexity of the disease genetic determinism. It is urgent to clarify the fact that, while in monogenic disorders a deleterious mutation is the key determinant, the majority of frequent diseases involve a combination of numerous genetic variations, such as SNPs, each conferring a very slightly increased risk, usually in the magnitude of 1.2, as measured by the numerous GWAS studies published over the last years. Second, the realization of a genetic analysis requires a specific, personalized information delivered before the test in order to explain the medical benefits of the test, the limits of the test and the medical consequences of a positive result, in terms of follow-up, investigations and treatment, not only for the tested individual but also for his family. Finally, the estimation of the genetic risk for an individual to develop a specific disease must be based on the evaluation of the phenotype and of the family history. Therefore, there is no evidence that 'positive' DTC tests, based only on the screening for common genetic variations, will justify a specific medical follow-up and procure a medical benefit to individuals. Furthermore, positive tests may induce psychological distress, even if the individual risk remains low. In contrast, 'negative' results might inappropriately reassure the patient concerning his risk to develop a disease. These limits and risks of DTC services are illustrated by one of the first studies on this topic published in this issue of the Journal.[2] This study has compared the performance of the personal genome screening (PGS) from Navigenics with the family history-based risk-assessment (FHRA) commonly used in genetic counseling sessions. A total of 44 participants were included in this study and their risks for breast, prostate and colorectal cancers were evaluated. FHRA classified 8, 2 and 7 patients as high-risk subjects for each cancer type, respectively, whereas 1, 2 and 0 subjects were classified as high-risk subject according to PGS. More importantly, PGS classified at high risk only 1 of the 9 subjects harboring a highly penetrant *BRCA* or colorectal cancer mutation.

After the revolution initiated by the next-generation sequencing, which has uncovered the extent of human DNA variability, revealed that diseases, initially considered as multifactorial, result in fact from *de novo* deleterious mutations and that disorders previously viewed monogenic may have an oligogenic inheritance, the challenge for medical geneticists is not anymore the detection but the interpretation of genetic variations. Our awareness of the complexity of the disease genetic determinism should lead more and more to a clinical guidance and a sophisticated interpretation. In this context, the development of DTCs appears as a paradox■

CONFLICT OF INTEREST

The author declares no conflict of interest.

1 Bloss CS, Darst BF, Topol EJ, Schork NJ: Direct-to-consumer personalized genomic testing. *Hum Mol Genet* 2011; **20**: R132–R141.
2 Heald B, Edelman E, Eng C: Prospective comparison of family medical history to personal genome screening for risk assessment of common cancers. *Eur J Hum Genet* 2012; **20**: 547–551.

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Carrier identification in newborn screening

Newborn screening for sickle cell disease: whose reproductive benefit?

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European Journal of Human Genetics (2012) **20,** 484–485; doi:10.1038/ejhg.2011.191; published online 9 November 2011

The ethics and policy statements about newborn screening (NBS) have routinely stated that the primary goal is to provide clinical benefit to affected children.[1–3] Although many policy statements acknowledge that NBS may provide reproductive information to the child and his or her parents, 'reproductive benefit' has always been viewed as secondary and not adequate by itself to justify screening of infants.

Bombard *et al.*[4] describe the findings from a sample of Canadian healthcare providers (HCPs) who were asked their attitudes towards the reproductive significance of identifying sickle cell carriers (known as sickle cell trait (SCT)) through NBS. Over two-thirds of HCPs who responded in the 2007 survey stated that they either 'agree' or 'strongly agree' that a purpose of NBS is to provide parents with information about their infant's carrier status (77.9%) of about the parents' own reproductive risk (68.1%).[4] The main justifications for this position are that reproductive risk information (1) allows reproductive choice and (2) permits disease prevention, a main goal of NBS.[4] On the other hand, a minority of health care providers suggested that it would be better to obtain reproductive knowledge in the preconceptional or prenatal rather than the neonatal period and that this should be done with a robust consent process.[4]

These findings are consistent with data from the mid-1990s when Wertz and colleagues[5] found that 74% of Canadian genetics services providers and 90% of United States primary care providers agreed with the statement 'An important goal of newborn screening is to identify and counsel parental carriers before the next pregnancy'.

The data show a broad disconnect between HCPs' goals and the preferences of the general public. Although SCT has been identified by NBS in the United States for over two decades (36 years in New York State), the frequency of sickle cell disease (SCD) among newborns has not appreciably changed.[6] Although NBS for cystic fibrosis is more recent, early data again show that reproductive information from NBS has had minimal impact,[7] as distinct from antenatal carrier screening.[8]

Bombard *et al.*[4] chose to focus their study on SCD, an autosomal recessive condition found mainly in minority communities in the United States and Canada. NBS for SCD is driven by the opportunity to save lives through penicillin prophylaxis and other clinical measures, and the detection of SCT is an incidental and unavoidable byproduct of screening. Thus, the HCPs may have been expressing a viewpoint that reproductive benefit is a 'free' additional benefit rather than expressing the viewpoint that reproductive benefit should be a primary benefit of NBS. If the researchers had truly wanted their respondents to focus exclusively on the legitimacy of reproductive benefits as a rationale for NBS, they should have used a condition like Duchenne muscular dystrophy or Fragile X for which early presymptomatic diagnosis is not known to provide clinical benefit to the infant but does offer reproductive information. Advocates of expanding NBS programs to include such conditions contend that there is benefit to the child—either in the avoidance of the diagnostic odyssey or in the ability to enroll in early research.[9,10] However, the same supporters also argue that there is a need to provide these services in the context of a robust consent process.[9,10]

The choice of conditions is further complicated by the 'not so benign' nature of SCT. Although the authors deliberately attempt to exclude the possible clinical implications of SCT, it is not clear that their respondents did so when answering the survey questions. Individuals with SCT are at increased risk of hematuria, hyposthenuria (decreased ability to concentrate urine), exertional rhabdomyolysis and splenic infarction with high altitude hypoxia.[11] These risks are moral justification for informing parents of their child's SCT, regardless of any reproductive benefit to themselves or their child.

Finally, the selection of SCT must be evaluated from a health care disparities perspective. In both Canada and the United States, the vast majority of women and couples with SCT are ethnic minorities. Both the potential benefits and adverse effects of carrier identification through NBS need to be carefully considered through close consultation with both HCPs and lay experts from at-risk communities. Although Bombard *et al.*[4] quote one participant who expressed this concern, it does not appear that the researchers specifically sought the opinions of the at-risk community to determine if SCT knowledge is a potentially real reproductive benefit or just a hypothetical reproductive benefit of essentially academic interest. Given the absence of North American data demonstrating that such information is indeed used for reproductive purposes, despite decades of both newborn and antenatal screening, the default assumption should be that this is not a real reproductive benefit. Neither the researchers nor the large majority of HCPs who agreed with the proposition that SCT detection is an important reproductive benefit have considered whether women and couples in at-risk communities would actually use that information in the way that many majority-community researchers and HCPs think that they should.

Bombard *et al.*[4] question whether it is appropriate to make reproductive information a primary goal of routine NBS, which is mandatory in most North American jurisdictions. In a previous article, the authors argue that any population screening program developed for reproductive benefit should either (1) incorporate a 'cascade of choices' meaning that the participants (or in the case of NBS, the parents) must have opportunities to consent to the testing or at least to decide whether to be informed of the finding or (2) focus on preconception or prenatal screening programs.[12] Assuming that the authors still believe that it is inappropriate to pursue reproductive goals outside of these two

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screening options, their current study identifies a critical need for educating HCPs about the ethically justifiable public health goals of a universal NBS program. Furthermore, researchers and HCPs must be culturally sensitive about the use of genetic information in reproductive decision making, particularly when the information is more frequently found in ethnic minority communities[13] ■

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ACKNOWLEDGEMENTS

I would like to thank Scott Grosse for his comments on an early draft of this essay. Dr Ross currently has grant support from the University of Chicago Center for Health Administration Studies and from the University of Chicago Comer Kids' Golf Classic to study the ethical and policy issues regarding the reproductive implications of sickle cell trait. Dr Ross also holds a Greenwall Foundation Grant to study The Clinical, Ethical, and Policy Implications of Sickle Cell Trait.

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