Morris JK, Law MR, Wald NJ:

Is cascade testing a sensible method of screening a population for autosomal recessive disorders?

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Cascade Testing for Autosomal Recessive Disorders

For some autosomal recessive disorders, unaffected carriers can be identified. Cascade testing is the identification of close relatives of an individual with a specific disorder to determine if they are also affected or carriers, and is an alternative to screening an entire (section of a) population. Morris et al. simulated a cascade testing program for autosomal recessive disorders with different carrier frequencies in a hypothetical population. They took the aim of cascade testing as the identification of offspring (pregnancies or children) affected by a particular autosomal recessive disorder and referred to these offspring as 'cases'.

After diagnosing a child (index case), both parents were identified as carriers (index couple) and all of their future offspring and (1) siblings only, (2) siblings and first cousins or (3) siblings, first and second cousins of both parents were tested. The program simulated 'extended family units' (= all people related to the index case) which differed in the frequency distribution of the number of children a woman had; of the probability being single or being in a couple with no, one or more children, and of the number of carrier couples and affected offspring. When a partner of a carrier appeared to be a carrier too, the 'extended family unit' of that person was also generated. The analyses differed in carrier frequency, strategy (1, 2 or 3; see above) and/or family size. A subsidiary analysis took consanguineous marriages into account.

The detection rate increased with the carrier frequency and whether testing extended to siblings, first and/or second cousins of identified carriers and the family size. The proportion of the entire population tested was in general small (advantage of cascade testing), but only a small proportion of all cases was detected. For example, using strategy 2 for cystic fibrosis (carrier frequency 4%), resulted in testing only 1.9% of the population, but would detect only 15% of all cases. The absolute risk of a related offspring being affected (the number of affected offspring identified divided by the number of related offspring tested) of this example is 1:313 and the likelihood ratio (increase relative to population risk) is 8. Even in populations where 50% of the marriages are consanguineous, the detection rates are still low (28.3% for a disorder with a carrier frequency of 4%).

High detection rates (80% or more) occur if the carrier frequency is high (>10%; for example β -thalassemia in some Mediterranean and southeast Asian areas), if strategy 3 is used at carrier frequencies over 4%, or if the family size is large. In these cases, as each index case has so many carrier relatives, cascade testing is very labor-intensive and expensive. Therefore, population screening would be the most preferable method anyhow. Morris et al. concluded that the performance of cascade testing is too poor to justify its introduction into practice as a screening test for autosomal recessive disorders.

Comments

Morris et al. showed that the intuitive expectation that cascade testing for autosomal recessive disorders should be effective is incorrect. Relatives of index cases have a much higher risk than the population risk, their likelihood ratio is increased, but detection rates (the proportion of affected offspring in the population identified through being related to an index case) are very low. For more common disorders, detection rates are correspondingly higher, but the population risk approximates the risks in the relatives. Based on the results of this study it can also be expected that neonatal screening of cases (homozygotes) with subsequent cascade screening will have the same low detection rate. Two groups preferred cascade testing for autosomal recessive disorders [1–3], but neither of these authors considered the low detection rates in their screening programs.

In contrast, cascade testing for autosomal dominant disorders can be an efficient method to detect relatives with these disorders, first of all because detecting a carrier means detecting a case. However, even for dominant disorders it will take many years to identify all carriers and therefore it may be too late to prevent related cases. For example, in a cascade screening program in the Netherlands for Familial Hypercholesterolemia (FH) the detection rate was in 2003, 9 years after starting the programme, 17,500 out of 40,000 [4]. Furthermore, the index cases of autosomal recessive as well as autosomal dominant disorders cannot be prevented by cascade testing at all, and when new mutations are common, the performance of cascade testing will be worse. Most of the difficulty lies in the initial step: the first identified individual has to be willing to give the addresses of his/her relatives. When probands decline to participate, their relatives will never have the test offered to them.

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Pilnick AM, Fraser DM, James DK:

Presenting and discussing nuchal translucency screening for fetal abnormality in the UK.

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Prenatal Screening for Down Syndrome: Talking About Risks

In the UK, prenatal screening for congenital defects of the fetus is a routinely offered procedure. Previous sociological and psychological research has tended to be critical of midwives in terms of ensuring informed choice in screening, but that research was based on post hoc accounts, according to Pilnick et al. The aim of this study was to investigate the relationship between information given by midwives and decision making by pregnant women offered nuchal translucency (NT) screening. The study focused particularly on how risk figures were discussed.

NT screening was offered to pregnant women in a large teaching hospital in the UK. In this qualitative study, 14 women were followed through the process of being offered NT screening and deciding whether or not to undergo this test, using data from three sources: tape recordings of pre- and post-screening consultations between midwives and pregnant women, and face-to-face interviews after the NT screening. Consultations and interviews were transcribed, coded and analyzed.

All of the participants had made their decision whether or not to undergo NT screening before their first consultation and they all decided to accept the offer of NT screening. From all pre-screening discussions about NT screening the midwives appeared to be at great pains to elucidate the nature of the result the NT screening would give. This emphasis on understanding the risk figures was also found in the post-screening consultations. In relation to the women's accounts of processing risk, some themes appeared to recur in the data. In the first place, external factors affecting risk perception (e.g. having had miscarriages and in vitro fertilization) were revealed. Secondly, some women showed a process of deliberation and decision making about possible future actions (like diagnostic testing) *before* undergoing NT screening, while others thought about the future in terms of 'crossing that bridge when we come to it'.

Pilnick et al. conclude that women should be encouraged to consider the possibility of an unfavorable result in advance of screening, to think about what they might want to do in that situation.

Comments

The authors state that their findings concerning the stress of midwives on ensuring that women understood the purpose, the potentials, and the drawbacks of NT screening are in stark contrast to previous work which has concluded that inadequate information was given to women beforehand or that women could not make sense of the results. Furthermore, the results are contradictory to previous studies on decision making and prenatal screening, in particular concerning the issue of informed choice. We should however bear in mind that this was a small qualitative study on 14 women in one teaching hospital.

Among others, Press and Browner have shown that in the USA prenatal screening is perceived as something self-evident [1–3]. However, Pilnick et al. doubt the findings of Press and Browner by suggesting that this is just a hypothesis by some critics, and that there has been little examination of actual consultation data to verify it. However, contrary to their claim, Press and Browner have also studied these actual processes: 'By observing the *specific process* (...) we have been able to shed light on how patient decisions are shaped' [1]. Furthermore, in other studies in which they presented a *content analysis of 40 prenatal intakes* and face-to-face interviews, Press and Browner revealed that no more than 20 min was ever devoted to the discussion of the screening test, and concluded that serum screening is presented as an uncomplicated and routine part of prenatal care [2, 3].

Recently, a systematic review by Green et al. [4] about psychosocial aspects of prenatal and newborn screening was published. This review included 106 publications (of which 78 were concerned with prenatal screening) from 12 different countries, for the most part the UK and the USA. Green et al. conclude that 'it is evident that women's understanding of screening is poor and not based on accurate evaluation of the decision-relevant information' and that 'most (women) are not making informed choices about screening'. These solid conclusions cannot be refuted by the qualitative analysis of consultations of only 14 women in the UK conducted by Pilnick et al. An interesting contribution to the debate however is the fact that women did not want to discuss, because they were determined before their visit to the antenatal clinic. This might explain why only few minutes are devoted to informed decision making, but has not received explicit attention in most studies so far. Furthermore, encouraging women to consider all possible outcomes of the screening test, including a positive result, is a significant remark. Strictly speaking, this topic should be broached in every pre-screening counseling session. When such a situation can be reached, then it is conceivable that prenatal screening decisions will become more informed choices.

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Hodge JG, Jr:

Ethical Issues Concerning Genetic Testing and Screening in Public Health.

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Bioethics and Public Health Ethics: Competing concepts?

This article focuses on the ethical issues that emerge within the context of public health applications of genetics. The argument starts from the assumption that a clear distinction exists between the concepts of bioethics and public health ethics. According to this position, bioethics largely focuses on the rights of individuals, whereas public health ethics focuses on the health of communities. The author holds the view that special principles of public health ethics are needed to justify voluntary genetic testing and screening and sharing of data for population-based health purposes, and that individual interests must be constantly balanced with the interest of society in the use of these data.

Assuming that genetic testing and screening further the public health goals of preventing and treating diseases in the population, a set of relevant ethical issues is examined. The questions addressed are concerned with individual informed consent, with the use of test results by authorities without violating individual and group privacy rights, with the justification of screening for every condition for which a reliable test is available, and with the voluntary versus mandatory character of screening programs. From the point of view of public health ethics, the author's main conclusions are that 'individual privacy interests in genetic information cannot be absolute, as others may have a right to know about an individual's genetic profile', and also that 'strict protection of autonomy, privacy and equal treatment of people with genetic conditions may threaten the accomplishment of communal goods, including public health surveillance.' The author admits that this position clearly challenges the widely accepted principles of mainstream bioethics with its strong focus on protection of the individual.

A further very important issue that is mentioned, is the concept of 'genetic exceptionalism'. This concept implies that genetic information as such is qualitatively distinct from other (medical) information and requires special standards of protection. The author, perceiving a legislative and policy trend towards genetic exceptionalism, puts forward various arguments against it. One argument is that, as the genetic background of more medical conditions is clarified, it becomes more difficult to distinguish genetic data from other medical data. Genetic information is part of the continuum of an individual's medical record. Another argument is that the greater protection

of genetic data can be counterproductive, as it may create public fears and misunderstandings, thereby discouraging people from seeking genetic testing or participating in screening programs. With regard to the USA, the author remarks that the varying level of protection of genetic data between the states hinders policy making in public health genetics.

Comments

This article sheds a very interesting light on the noted conflict between individual and communal interests, a conflict that has recently drawn attention in several community genetics debates [1, 2]. This conflict of interests is underlying the difficulties in the moral justification of public health concepts. However, it is questionable whether the introduction of a concept of community ethics or public health ethics *as opposed to* bioethics can resolve the problem. The conflict is intrinsic because individuals are always also members of communities and communities by definition consist of individuals. Even if mainstream bioethics starts from the individual, and the protection of individual rights and interests, much attention is devoted to formulating the conditions upon which individual rights may be overruled in the interest of others. Neither individual autonomy, nor individual liberty can be regarded as absolute but are subject to balancing [3]. In particular, a breach of professional confidentiality can be justifiable in cases where keeping silent would cause serious harm to others. These others may be family members, e.g. in the context of clinical genetics, or they may be members of a population, where in particular in the context of controlling communicable disease even coercive measures can be justified. The latter case is a clear example of bioethics being applied to a public health problem.

The discussion about genetic exceptionalism shows that ethical and legal thinking, and the implementation of regulation are not keeping pace. As genetic testing became part of established clinical practice in many places, special rules for genetic data protection were designed and are currently being implemented. However, in the genomics era, policymakers are being advised by lawyers and ethicists to give up genetic exceptionalism and to establish instead special protection for any health data with high information content [4, 5]. This is also the position held by Hodge Jr.

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