

Ethical problems with neonatal screening

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Summary. The availability of novel technologies, such as tandem-mass-spectrometry (MS/MS) and DNA analysis, has expanded tremendously the number of genetic conditions that can be diagnosed through neonatal screening programs at birth, including conditions that cannot be treated nor prevented, or that will become manifest only later in life, or that identify individuals that are only at an increased risk of multifactorial conditions. This has increased the number and complexity of ethical problems related to newborn screening programs, creating considerable confusion and generating controversies and ethical concerns. The experience so far gained indicates that, besides the incomplete knowledge of many aspects of the conditions to be identified, the majority of screening programs do not pay sufficient attention to the problems of communication, information and counselling of the parents. Therefore, communication must be substantially improved if we wish to increase the efficiency of such programs and avoid possible unwanted side effects. Furthermore, ethical issues should receive more attention and consideration for a better and more complete understanding of the overall impact of neonatal screening programs. This more extensive and ethically correct approach should allow us to find an optimal equilibrium between the potential benefits and the possible damages deriving from neonatal screening programs.

Key words: neonatal screening, ethics, communication.

Riassunto (*Problemi etici connessi agli screening neonatali*). La disponibilità di nuove tecnologie, come la spettrometria di massa in tandem e l'analisi del DNA, ha aumentato enormemente il numero di condizioni genetiche che possono essere diagnosticate tramite i programmi di screening alla nascita: è attualmente possibile identificare malattie che non possono essere curate né prevenute, o che si manifestano solo in età più avanzate, o soggetti che presentano solo un rischio aumentato di contrarre malattie di origine multifattoriale. Tutto ciò ha aumentato il numero e la complessità delle problematiche etiche relative ai programmi di screening neonatale, creando una certa confusione e generando controversie e preoccupazioni di ordine etico. Le esperienze finora raccolte suggeriscono che, oltre alla conoscenza incompleta di molte delle condizioni che possono essere identificate alla nascita, la maggior parte dei programmi di screening neonatale non presta sufficiente attenzione ai problemi di comunicazione, informazione e consulenza dei genitori. Pertanto la comunicazione deve essere molto migliorata se si vuole aumentare l'efficacia dei programmi di screening alla nascita ed evitare spiacevoli effetti collaterali. Inoltre le questioni etiche devono ricevere maggior attenzione e considerazione per una migliore e più completa comprensione e valutazione dell'impatto globale dei programmi di screening alla nascita. Questo approccio più completo ed eticamente più corretto dovrebbe permetterci di trovare un equilibrio ottimale tra i potenziali benefici e i possibili danni derivanti dai programmi di screening neonatale.

Parole chiave: screening neonatale, etica, comunicazione.

INTRODUCTION

Ethical issues have gained increasing attention in the present era of outstanding scientific and technological advances and enthusiasm. Indeed, the overwhelming pressure of technology has induced us to consider more carefully what we have the possibility and the power of doing and what in fact we decide to do in practice, and to evaluate carefully if what we finally do is really for the good of the individual and of mankind in general, *i.e.* it is ethically correct and justified.

The traditional and oldest neonatal screening programs, such as those for phenylketonuria (PKU) and congenital hypothyroidism (CH), have gained wide acceptance all over the world and nobody will argue today that they represent a major advancement in public health. In fact, they are probably the most efficient and effective of all screening programs so far implemented; they have saved and continue to save thousands of children from death or severe brain damage; furthermore

they are cost-effective, *i.e.* they save money for the society. In fact the screenings for PKU and CH have set the standards to which any neonatal screening program should comply.

Ten criteria (Wilson-Jungner criteria) have been endorsed by the WHO for the applicability of any screening program:

1. the condition sought should be an important health problem;
2. there should be an accepted treatment for patients with recognized disease;
3. facilities for diagnosis and treatment should be available;
4. there should be a recognizable latent or early symptomatic stage;
5. there should be a suitable test or examination;
6. the test should be acceptable to the population;
7. the natural history of the condition, including development from latent to declared disease, should be adequately understood;
8. there should be an agreed policy on whom to treat as patients;
9. the cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
10. case-finding should be a continuing process and not a "once and for all" project.

Four of the above criteria are particularly relevant to the problems here discussed:

- *knowledge of the disease.* Before we implement a screening program we should know well all the features of the disease or condition to be screened: its incidence and prevalence in the population, as well as its clinical picture and natural course;
- *knowledge of the test.* The reliability of the testing procedure must have been fully evaluated: its sensitivity (false negatives rate), specificity (false positives rate) and predictive value should be known and constantly monitored;
- *treatment of the disease.* The condition or disease to be screened should be amenable to effective treatment or should have a latent phase during which appropriate interventions can prevent damage;
- *cost considerations.* Finally, the program should be economically sustainable. In all Countries the resources allocated to the health system are not infinite and any screening program must compete successfully, also from the economical point of view, with other potentially useful programs or interventions.

These criteria are still valid today. However, the scientific progress and the availability of new technologies have increased tremendously the number of conditions that can be subjected to neonatal screening. This has considerably complicated the situation, introducing new problems and highlighting many controversial issues, some of which may have important ethical implications.

Many questions need to find a satisfactory answer and are still a matter of debate today.

Which disorders should be screened among the numerous possibilities now available? And how should we proceed in including or deleting some tests from a screening program? What laboratory methods should we choose and how are we going to assess its validity and assure quality-control? How are we going to regulate this process and what kind of legislation should be enforced? How should we deal with the critical issues of communication and parental consent or dissent? What criteria should be used to evaluate the validity of new expanded screening programs? And, above all, who should make these and other critical decisions?

Numerous expanded neonatal screening programs have been implemented in various Countries, without answering many of those questions and this is reflected in the considerable variability of those programs. For example, in the USA and in other Countries, the number of conditions screened in the different States or Regions can range from less than 8 to over 40! Furthermore, the parents' involvement and the attitude towards the need of parental informed consent vary considerably from State to State, as well as among the different Countries in the world. Of course, many of those questions are relevant to any screening program; however, they are particularly crucial in the case of neonatal screenings, due to the peculiarities of genetic testing in newborn infants.

Indeed, compared to other screening programs, neonatal screening has some features that may have special ethical relevance:

- the genetic information that is generated does not affect solely the infant, but has important implications for the whole extended family;
- some risks of neonatal screenings may not be obvious at first glance, since they are mostly psychological, social and economical in nature;
- in the case of expanded screening programs, including susceptibility testing, the predictive power is low and the preventive actions that could be implemented have limited and controversial value;
- for many of the conditions that can be diagnosed at birth there are no preventive or curative treatments or interventions available at the present time;
- finally, the child, and often also the parents, cannot participate in the decision making process.

Some of those aspects can also pertain to other screening programs: however, what is unique of neonatal screening is that they may be all present at the same time. This increases considerably the complexity of the issue and has some ethical implications that we shall discuss in a moment.

THE BASIC PRINCIPLES OF BIOETHICS

Before discussing the specific ethical problems generated by neonatal screening programs I wish to summarize briefly the most important ethical prin-

ciples that form the basis of our medical decisions, including planning and implementing a screening program:

- *non maleficence*. This principle is included in the Hyppocrates' oath, *primum non nocere*, that is "first do no harm"; in other words never damage your patient, which, in our case, is not only the child, but also the parents and the whole family;
- *beneficence*. This is the symmetric counterpart of the previous one; make sure that you act for the good, for *the best interest*, of your patient;
- *autonomy*. This is a relatively new principle, typical of modern democratic societies. Your medical acts must be negotiated and be in accordance with the patient, who can consent or refuse. To be able to exert his/her autonomy the patient must be adequately informed (informed consent/dissent, patient's empowerment);
- *justice*. This is the most ambiguous of the four principles and may generate confusion: which justice should be followed? Moral? Legal? Religious? Economic?

It is also obvious that in order to comply with these principles physicians have at least two other obligations:

- *knowledge*. They must have full knowledge and understanding of the problem or the condition that they are facing and of the features and consequences of the screening program implemented;
- *communication*. They should be able to communicate efficiently with the patient or the parents, and also with the community and among themselves.

It is immediately apparent that these fundamental ethical principles mimic closely the four WHO validity criteria for a screening program. Knowledge (of the disease and of the test) is essential for satisfying the first two principles (non-maleficence and beneficence); treatment or prevention of the disease is entwined with beneficence and knowledge; cost considerations are relevant to the principle of justice and to the fair distribution of resources; and communication is essential for autonomy as well as for optimal treatment (beneficence).

It is also intuitive that these same principles can enter in conflict with one another and thus generate an ethical dilemma.

For example, justice (*i.e.* a balanced distribution of resources) could be fair for the society but could be in contrast with the best interest of a single patient; the results of a screening test could be beneficial for the child (beneficence), but produce damages to other members of the family (maleficence); the full exercise of autonomy by the parents (refusal of the test or request of a useless one) could be deleterious for the child (maleficence).

We shall consider four of the ethical concerns or controversies generated by neonatal screening programs: that pertaining to the role of parents and to the issue of informed consent/dissent; the one related to the intrinsic characteristics of the test,

and particularly to its specificity, and to the consequences of false-positive results; the issue related to the screening of healthy, asymptomatic carriers of a genetic condition; and finally the controversies regarding the expanded screening programs, *i.e.* those for diseases that can neither be prevented nor treated, or diseases that will become manifest much later in childhood or in adult life, or genetic susceptibility programs, that are aimed at the identification of patients who are at higher risk for a multifactorial/polygenic disease than the general population.

THE QUESTION OF INFORMED CONSENT

Informed consent and the right to refuse is a central ethical issue in screening programs for the adult population. It is also central for neonatal screening, though in the latter case the consent must be given by proxy, *i.e.* by the parents. This has raised considerable controversies, as is reflected in the wide variability at both policy level and in the practical delivery programs of different Countries.

The principal ethical justification for mandatory screening is the claim that society's obligation to promote child welfare through early detection and treatment of selected severe conditions supersedes parental prerogatives to refuse a simple medical intervention.

An opposing argument maintains that parents traditionally have broad discretion in making health care decisions for their children.

Screenings, such as PKU and CH, which are clearly beneficial and with minimal side effects, are considered by the WHO guidelines as sufficiently important to override parental consent and should be mandatory and free of charge for all Countries. In some USA states and in many other Countries these screenings are offered on an "opt-out" basis, whereby parental consent is assumed if no objections are voiced. This position is not optimal but it can be ethically acceptable.

In any case adequate parental information is considered of paramount importance for the success and for the ethical acceptability of any newborn screening program: however, the experience shows that this obligation is not always well respected and that the information provided is often minimal or insufficient.

On the other hand, there are potential advantages in including informed consent in neonatal screening programs: the response to a positive test result is more prompt and efficient; the parents express their appreciation; there is the possibility of adding new experimental tests to the well established ones. Furthermore, the few programs that have incorporated parental informed consent, have registered a remarkably good compliance: the refusal rate has been less than 5 per thousand and the consent process took only 5 minutes of staff time.

For those programs that incorporate screenings of more controversial value, such as those for late-on-

set diseases, or for diseases that cannot be treated nor prevented, or for multifactorial conditions, the offering of the test should be on an optional basis and parental informed consent should be mandatory.

THE CHARACTERISTICS OF THE TEST

The problems related to the characteristics of the test employed for screening are also important.

Imperfect sensitivity, *i.e.* the occurrence of false negative results, is intrinsic to any laboratory test and therefore must be accepted. This is taken into account when a new screening program is implemented and the rate of false negative results is usually kept at a very low level. Therefore, this does not represent an important ethical issue.

Much more important and of greater concern are the problems related to the specificity of the testing procedure, *i.e.* those deriving from a false positive result.

The need of assuring a high sensitivity of the test, in order to identify all the affected individuals, inevitably produces a lower specificity and thus a higher rate of false positive results.

The damages produced by a false positive test are often overlooked, since they are usually psychological in nature and sometimes difficult to recognize. Increased parental stress, depression and anxiety are frequent and can persist in time, resulting in long standing disturbances of the parents-child relationship, such as the "vulnerable child syndrome". There could be a persistent misunderstanding of the child's risk of developing the disease, with an increased and inappropriate resort to medical attention and hospitalization. Parental reproductive decisions can also be influenced by a false positive result. Therefore, good communication with the parents is of paramount importance, since many problems can be prevented by adequate information before and after the test's results.

SCREENING FOR THE CARRIER STATE

Some of the problems generated by a false positive result are also common to the screening of a carrier state for a recessive genetic disease. A carrier could be identified by chance, as a result of an established screening program for affected subjects, such as that for cystic fibrosis (CF), or be included in a specific screening program or upon request by the parents.

The identification of an asymptomatic carrier of a recessive genetic condition could have some theoretical advantages in that it would allow prospective parents to make a more informed reproductive decision. This, of course, is also possible for the healthy carrier himself, who could use this information later on in life.

However, there are also many drawbacks. The carrier state is often misunderstood by the parents and by the public in general. Confusion about the dif-

ference between being a healthy carrier of a genetic condition and being truly affected with that condition may lead to parental anxiety and distortion of the parents-child relationship, as well as to social stigma and discrimination. The possible deleterious consequences for the child and the family are obvious. Furthermore, it remains to be determined whether the results of a test performed in the newborn period will really be utilized effectively many years later, when the individual will make reproductive decisions.

For all those reasons, screening of a carrier state in newborn infants, and in young children in general, is ethically unjustified, while it is perfectly justified in adults when is offered on a voluntary basis and is accompanied by appropriate information and genetic counselling.

On the other hand, when a newborn infant is identified accidentally as a healthy carrier of a genetic condition, it may be appropriate to carefully inform the parents after obtaining their consent and to provide adequate information and counselling.

EXPANDED SCREENING PROGRAMS

The availability of novel technologies, such as tandem-mass-spectrometry (MS/MS) and DNA analysis, has expanded tremendously the number of genetic conditions that can be diagnosed at birth. This has created considerable confusion and generated some controversies and ethical concerns.

Firstly, there is no doubt that increasing the number of tests will also increase the number of false positive results and we have already discussed how this can damage the child and the whole family.

Secondly, many of the diseases that can be diagnosed at birth are presently not preventable nor curable and therefore there is no clear advantage for the child deriving from their early detection.

And finally, some of these diseases, such as, for example, Duchenne muscular dystrophy, will become manifest only much later in life and nothing can be done to delay their onset.

Those who promote expanded screening programs maintain that they will improve our knowledge of the incidence and the natural course of the disease and provide useful information to the child's parents and relatives to make their reproductive decisions. Furthermore, in case of late-onset diseases, there is always the possibility that new preventive measures will be discovered and in that case a registry of pre-symptomatic patients might prove useful for an earlier intervention.

The objections to that position are similar to those already discussed for the screening of carrier state: parental anxiety and distress, impaired parents-child relationship, social stigma and disturbances in child's development. Furthermore, there is some worry that they would increase excessively the utilization of resources at the expenses of more useful and less controversial interventions.

If a program of this kind is considered for neonatal screening, then before it is implemented it must be preceded by a carefully planned experimental phase, aimed at evaluating all the potential benefits and unwanted side effects for the child, the family and the society as a whole. If the results of this experimental phase support the opportunity of implementing such a program, then it should be only offered on a voluntary basis, after informed consent by the parents, and be accompanied by adequate counselling and support to the parents of the affected child.

However, it is doubtful that expanded screening programs for late-onset and incurable diseases can be recommended on ethical grounds.

Similar and more stringy considerations are also pertinent to neonatal screening programs for the genetic susceptibility to multifactorial/polygenic diseases. These screenings are aimed at the identification of subjects that have an increased genetic risk of developing a clinically significant condition. The results are usually expressed in statistical terms, such as probability estimates, odds ratios or risk ratios, and have a high degree of uncertainty, due to the wide variations of the interactions between genes and environment. It is uncertain that the child will really develop the disease and, if this were the case, at what age the disease will appear and how severe it will be.

The advantages and disadvantages of genetic susceptibility testing derive from the above considerations.

The possibility of modifying the natural course of diseases, such as type-1 diabetes or familiar hypercholesterolaemia, by preventive measures, is so far controversial. Also, the possibility for the parents to prepare themselves emotionally and to improve their ability to identify earlier the clinical signs of their child's disease is doubtful.

On the other hand, the majority of high risk children will never develop the disease and nevertheless they and their parents will be subjected to undue psychological pressure and concern, while, on the contrary, some low risk children will in fact develop the disease and the diagnosis could be delayed by a false sense of security of their parents deriving from a negative predictive test.

Furthermore, the compliance to the eventual preventive measures is uncertain and sometimes could be excessive and inappropriate.

Finally, there is the substantial risk of creating a new category of pseudo-patients (pre-patients, worried-well), with the obvious psychological consequences for the child and the parents and the realistic possibility of social stigma and discrimination (*i.e.* by employers or insurance companies).

On the basis of the above considerations, genetic susceptibility testing in newborn infants cannot be recommended on ethical grounds.

However, it can be offered to the adult population on a voluntary basis, after informed consent, and be followed by adequate genetic counselling.

PRESENT POLICIES

In view of the enormous possibilities provided by the introduction of MS/MS the American College of Medical Genetics (ACGM) published a document in 2005 (*Newborn screening: toward a uniform screening panel*) which had a great impact on the organization of neonatal screening programs in the USA.

In this report the ACGM made a critical analysis of all the genetic conditions that could be identified by MS/MS. For 30 of them they found no reason to be included in a neonatal screening program. The other 54 candidates were subdivided into two groups: 29 "core" conditions, for which neonatal screening was highly recommended, and 25 "secondary" conditions that could also be included in a neonatal screening program.

It must be stressed that the above recommendations are not completely in line with the classical Wilson-Jungner criteria, particularly with the requisite that the patient (newborn) should derive a sure benefit from such screening, since many of the core and secondary conditions are not amenable to treatment. Other criteria were used by the ACGM, such as the advancement in scientific knowledge, a better understanding of the natural history and epidemiology of the condition studied and the fact that the results are provided anyway by MS/MS without added costs.

It is notable that at the same time a similar analysis performed in the UK concluded that, compared with traditional screening, MS/MS could be indicated and cost-effective only for two disorders, PKU and medium-chain Acyl-CoA dehydrogenase deficiency (MCAD).

Recently the ACGM report has been strongly criticised on ethical grounds by the President's Council of Bioethics, since it does not comply with the classical and still valid Wilson-Jungner criteria. The Council pointed out that the principle "screen only if you can effectively treat" seemed to have been replaced by a new principle "screen unless there is a compelling reason not to screen" and that this change cannot be justified on ethical grounds. The Council strongly recommended that the USA states should incorporate in their mandatory screening programs only those conditions that meet the classical Wilson-Jungner criteria and in particular the availability of an effective treatment. Screening for any other disorder should be offered only on a voluntary basis, under a research paradigm and after appropriate information and consent by the parents.

It is instructive to analyze the present situation of neonatal screening *vis a vis* with the four ethical principles at the basis of medical practice:

- *non maleficence*. The unwanted side effects for the child and the parents, deriving by the indiscriminate application of some kinds of screening (healthy carrier, conditions with delayed onset, multifactorial disorders) are significant and often underestimated. Furthermore numerous studies have demonstrated that physicians have a limited

knowledge of the advantages and disadvantages of the various types of screening and are unable to provide adequate information to the parents.

- *beneficence*. The benefits for the child of some screenings (such as PKU, CH, galactosemia and MCAD) are undeniable. However, other types of screening (such as carrier state, lethal conditions, disorders with delayed onset and susceptibility testing) are of no or disputable benefit for the child;
- *autonomy*. Since newborn infants are incompetent, the choices are delegated to the parents who are generally inadequately informed; furthermore their opinion and consent is often not requested. Therefore they are not in the condition of making a real autonomous choice;
- *justice*. The advantages for the society of some types of screening are absent or doubtful. There is a remarkable geographical heterogeneity in the different screening programs with consequent unjustified unequal opportunities for the population.

CONCLUSIONS

In conclusion, the availability of new and more sophisticated diagnostic procedures, such as MS/MS, has expanded considerably the number of congenital disorders that can be diagnosed through neonatal screening programs, including the possibility of identifying individuals at risk of multifactorial conditions.

This has increased the number and the complexity of the ethical problems related to newborn screening programs.

The experience so far gained indicates that the majority of the screening programs do not pay sufficient attention to the problems of communication, information and counselling of the parents, as well as to

the medical community and the public in general. Therefore, communication must be substantially improved if we wish to increase the efficiency of such programs and avoid possible unwanted side effects.

For many of the conditions that can be identified at birth the natural history and the clinical significance is still poorly understood; also, preventive and therapeutic measures are not presently available.

Much to often the availability of sophisticated technological tools is interpreted as a moral obligation to utilize them. This can produce profound changes in the ethical models that have accompanied us since the beginning of neonatal screening, that is a shift from the need of undisputable direct benefits for the individual (newborn) to a hypothetical societal benefit (research, scientific progress, better knowledge). This is in contrast with the long-standing ethical imperative, first enounced by Claude Bernard, that an individual cannot be utilized without his or her consent for research that would generate a benefit to others and not to him or her.

Neonatal screening programs provide a good example of the ethical problems generated by the potent technological instruments presently available and by the profound impact that they can have on the way we practice medicine today. Technology must be appropriately governed and be at the service of medical practice without prevaricating other important individual and social values.

Not everything that can be done should be done (and many important things that are not presently done should receive better consideration!).

This more extensive and ethically correct approach should allow us to find an optimal equilibrium between the potential benefits and the possible damages deriving from neonatal screening.

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