

# Conceptual issues for screening in the genomic era - time for an update?

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## ABSTRACT

**BACKGROUND:** Screening tests are ubiquitous in modern medicine; however a consensus view on the criteria that distinguish screening from clinical testing remains strangely elusive. Although numerous definitions of screening have been suggested, there is considerable variation amongst them, leading to confusion and disagreement amongst clinicians and public health professionals alike. In light of developments in genomics, the question of what screening entails is becoming increasingly pressing.

**METHODS:** We evaluated the concepts underlying definitions of screening versus clinical testing and investigated their ethical implications.

**RESULTS:** We suggest that just two key concepts underlie screening: first, screening tests are performed in *asymptomatic* individuals and, second, they are generally *offered* to individuals who otherwise believe themselves to be healthy (with respect to the disease being screened for). All the other characteristics commonly invoked to describe screening - including the systematic use of rapid tests for risk stratification within a particular population - can be better categorised as either practical requirements or by-products of screening programmes rather than screening tests.

**CONCLUSIONS:** We emphasise the need to differentiate between opportunistic screening and clinical testing because of the differing prior probability of disease and thus the differing ethical burden of responsibility placed upon the physician in each scenario. Physicians need to appreciate the shifting moral burden placed upon them in relation to reactive clinical testing versus proactive screening, and the different legal obligations that may ensue.

*Key words: screening tests; genomic era; clinical tests*

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## INTRODUCTION

There is considerable debate surrounding the concept of screening[1] and its application,

evaluation and categorisation[2]. Screening has historically been concerned with prevention of disease by early detection, whilst clinical medicine concerned itself with diagnosis based

on presenting symptoms. A paradigm shift in clinical medicine is now beginning, partially brought about by advances in genomics and molecular biology, and the rhetoric is away from an age of diagnosis and treatment and towards an era of prediction and prevention. Within the context of the rapidly evolving field of genomics, terms like 'genetic screening' and 'genome scans' are becoming common parlance; in addition, there has been a proliferation of 'health screening' services offered directly to the consumer. Moreover, recent recommendations from the American College of Medical Genetics and Genomics (ACMG) propose that all clinical genome-wide sequences should be routinely screened for a list of specific diseases[3] without explicitly and separately seeking consent for screening for each of the included disorders.

The potential for simultaneous provision of diagnostic and predictive tests leads to complexities around when tests should be categorised as screening, what level of predictive or diagnostic accuracy we should expect from them before implementation, and how they should be interpreted. The purpose of this paper is not to question or review the principles that should govern a national screening programme, as proposed by Wilson and Jungner[1]; rather, we aim to interrogate the key concepts involved in all acts of medical screening and to outline a conceptual framework for thinking about screening in the future.

It is useful at the outset to make a distinction between an *assay*, the scientific measurement of a biomarker (e.g. sequencing a genome), and a *test*, its application and interpretation within a particular context[4]. Importantly, while evaluation of an assay can essentially be a unidimensional measure of technical accuracy, there are an additional three dimensions to test evaluation: the specific disease, the target population, and the purpose of the test. The same assay can therefore be used for numerous different tests, with varying degrees of success. Although the analytical validity of the assay is completely independent of its clinical usage, the clinical validity and utility of a test – and therefore its effectiveness within a health care setting – is highly dependent upon its purpose and the context in which it will be used[5]. For example, a genetic variant may be the cause

of one disease but only weakly associated with another; similarly, a genetic variant may be highly predictive in an affected family but only weakly predictive if found in the general population. In addition, utility has a subjective element, and a test of any given clinical validity may be perceived by different individuals to have greater or lesser clinical utility.

We suggest that the ultimate aim of any medical test is to allow a decision to be made about an appropriate management that might serve to delay the onset or reduce the burden or severity of disease, whether this be through risk prediction, early detection, diagnosis, prognosis, or response to treatment. Diagnosis, in this sense, is no more than a shorthand for referring to the patient's condition that will allow the symptoms and signs of the condition, as well as its prognosis and response to treatment, to be categorised by the physician. When a patient presents with a particular problem the physician attempts to elucidate its cause by taking a history, conducting an examination and carrying out a series of tests. Tests carried out in this context are normally referred to as diagnostic tests. The purpose of the test(s) is to seek a diagnosis for the patient's problem, and the test result is interpreted in the context of the patient's clinical presentation.

However, tests may also be carried out in situations where the patient does not complain of any problem, but when the physician explicitly and intentionally seeks to determine if the patient has a disorder unrelated to the presenting complaint. These tests are called screening. There are essentially two contexts in which screening tests are traditionally encountered: ad hoc when a patient visits his or her physician with an unconnected issue (*opportunistic screening*) [6, 7], or through a formal screening programme offered proactively to a population (*invitational screening*). In the former, although 'incidental findings' may be accidentally uncovered through the course of diagnostic testing, opportunistic screening may also occur if the intention is to look explicitly for unrelated disorders.

In contrast to opportunistic screening, a screening programme is a public health service, usually organised at a national level, with the purpose of reducing overall morbidity or

mortality from a particular disease. It attempts to systematically identify a specific population considered to be at increased risk of a particular disease. The programme provides a joined-up pathway to secondary prevention, from identification of a particular subpopulation for screening, through to follow-up diagnostic testing for screen-positive individuals and ultimately treatment for those who need it. [An important subset of screening programmes are those offered in the context of antenatal screening, to provide information on the health of the foetus and to enable parents to exercise reproductive choice about whether or not to continue the pregnancy. The primary purpose in these circumstances is the wellbeing of the parents and the family. The special circumstances of such programmes, and the specific issues that they raise, will not be further discussed in this paper.]

Given the increasingly common occurrence (but variable usages) of the term 'screening' in medical and scientific literature, as well as the popular press, we pose the following questions: is there a distinction between screening (whether opportunistic or invitational) and clinical testing? And if so, what are the implications?

## METHODS

We carried out a review of nine representative sources of definitions of screening (see Table 1) to identify common elements. We then examined the criteria that are essential to defining screening and investigated their implications for clinical practice.

## RESULTS

Criteria for defining screening versus clinical testing can be classified into six separate descriptions of 'screening':

1. a test performed on *asymptomatic* individuals;
2. a test used for *risk stratification*, rather than diagnosis;
3. a test *offered* (either by a physician or the health care system) to a patient or citizen rather than actively sought by the patient;
4. a test applied to a *population* or

subpopulation, rather than on the basis of an individual clinical evaluation;

5. a test applied *systematically*; and
6. a test applied *rapidly*.

The nine definitions of screening examined here vary in their inclusion of these criteria (see Table), raising the question of which characteristics are essential for a screening test. The last three criteria (4-6 above) are absent from the majority of the definitions of screening (Table), in our view, because they are specific to screening *programmes* rather than screening tests. A screening programme must be offered, in a systematic and explicit manner, to the specific subpopulation at highest risk of the disease in whom testing is likely to be most beneficial in order to maximise its effectiveness and to ensure equity. Administrative arrangements are usually established to promote the screening programme, encourage the target population to attend and to collect data on the activity, including uptake rates and outcome of the programme; targets are set and activity and outcomes are monitored against those targets. Additionally, for purely practical purposes, the tests used in a screening programme are usually rapid to apply, easy to carry out, safe and inexpensive. We therefore confine our discussion about the distinction between screening tests and clinical tests to the first three criteria (1-3 above).

## DISCUSSION

### (1) *Asymptomatic Individuals*

The first of these requires that the test be carried out on asymptomatic or healthy individuals with respect to the disease being screened for. (In the case of opportunistic screening, the individuals present with symptoms that are unrelated to the test being offered). This is the only criterion included in all the definitions of screening reviewed here. Unlike clinical testing, which is initiated in order to determine the cause of specific symptoms or as a result of a medical history, screening tests are carried out prior to the development (or reporting) of symptoms.

The ethical burden upon the physician is therefore generally considered to be

TABLE 1

INCLUSION OF THE SIX KEY ELEMENTS IN NINE SOURCES OF INFORMATION ON 'SCREENING' (IN CHRONOLOGICAL ORDER)						
SOURCE	ASYMPTOMATIC	RISK	OFFERED	POPULATION	SYSTEMATIC	EASY/RAPID
WHO (from US Commission on Chronic Illness, 1951)[10]	x	x				x
Sackett & Holland (The Lancet, 1975)[7]	x	x		x		
Morrison (Screening in Chronic Disease, 1985)[11]	x	x				
Fletcher, Fletcher & Wagner (Clinical Epidemiology, 1996)[12]	x					x
Cuckle & Wald (Antenatal and Neonatal Screening, 2000)[13]	x	x			x	
Grimes & Schulz (The Lancet, 2002)[14]	x	x	x			
Oxford Handbook of Public Health Practice (2006)[15]	x	x	x	x	x	
Rothman, Greenland & Lash (Modern Epidemiology, 2008)[16]	x					
UK National Screening Committee (www.nsc.nhs.uk)*	x	x	x	x	(x)	

x indicates that the word in the top row is used (or implied) in the definition

(x) indicates that the term 'public health' is used in the definition, which is assumed here to imply the application of a test in an organized or systematic manner at a population level

\* Accessed 11 November 2014 at <http://www.screening.nhs.uk/screening>

greater for screening than clinical testing, as screening is performed on apparently healthy individuals. There is therefore significant potential to do more harm than good through overmedicalisation. This distinction is also important for understanding the predictive value and utility of the test, which are related not only to the technical and clinical accuracy of the test, but also to the Bayesian prior (and therefore posterior) probability of the disease in the individual being tested. The pre-test probability, and consequently the post-test probability, of an individual seeking a test as a result of symptoms or medical history will usually be higher than that of an asymptomatic individual. Given a high prior and/or a highly accurate assay, a diagnostic test will produce a sufficiently high posterior that further testing is not required; in contrast, given a low prior and/or a poorly performing assay, a screening test will result

in a correspondingly lower posterior that requires follow-on confirmatory testing.

In the context of genomics, most genes known to cause disease have been found through clinical testing of affected individuals and families. Therefore, the population penetrance of even well established, clinically-ascertained diagnostic variants is unknown, making interpretation of the results of genomic screening extremely challenging[8]. [We suggest that the practice of testing family members of patients with known genetic disease should more properly be referred to as cascade testing rather than cascade screening, because of the relatively high pre-test probability in these individuals.] Since every test has a risk of misclassification of disease, and the chances of doing harm through overdiagnosis, follow-on *testing* and unnecessary treatment – potentially cascaded out through the family – is vastly increased when 'healthy'

individuals are screened opportunistically for multiple diseases[9].

## (2) Risk Stratification

The second criterion, found in most but not all of the definitions studied, suggests that the purpose of the test is to stratify the population into higher and lower *risk* groups, rather than to make a precise diagnosis. Within a medical context, the word 'risk' can have two possible meanings: first, the probability of developing a disease in the future; and second, the probability of having a disease currently. The former – tests that seek to assess the risk of future disease – are in effect tests for risk factors. Examples include blood pressure and cholesterol level as well as genetic variants that affect the risk of disease. These aim to provide a *prediction* of future events, and are subject to numerous interactions and stochastic processes that affect the accuracy of the prediction. A raised blood pressure or cholesterol raises the probability of stroke or heart attacks, but they are not measures of whether or not a heart attack or stroke has occurred. As we continue to improve our understanding of the disease process at the molecular and genetic level, prediction of the risk of future disease is likely to become more accurate and increasingly commonplace in clinical and public health practice. But for these predictive tests, there is no way by which the clinical validity of the test can be determined at the time of testing since, by definition, the disease process has not yet been established. Since the population tested in this pre-disease scenario is asymptomatic, arguably this criterion can be subsumed under the previous one with respect to screening, and all the caveats relating to disease prediction and harms versus benefits apply.

By contrast, tests that seek to provide an early diagnosis of existing sub-clinical disease, before the development of symptoms or signs of disease, use biomarkers that can demonstrate the presence of subclinical disease. In these situations, the 'risk' of disease simply reflects our degree of belief in the test itself (i.e. the probability that the individual actually has that disease), which relates to its predictive ability. This is a function of the prior probability of disease and the sensitivity and specificity of the test used for disease detection (specifically

its likelihood ratio). Within a typical classical screening programme, an imperfect biomarker is commonly used (necessitated for practical purposes), which discriminates poorly between diseased and non-diseased cases, leading to numerous false results (both positive and negative). Coupled with the low pre-test probability of disease in asymptomatic individuals, the results of such a test rarely lead in practice to a definitive diagnosis (i.e. a high post-test probability of disease), and a follow-up diagnostic test is usually required. However, if the true intention were actually early diagnosis of a clinically important disease, a theoretically perfect test would not necessitate further confirmatory evidence and could arguably be diagnostic on its own.

Advances in genomics and molecular biology are now yielding novel and increasingly accurate biomarkers as well as highly sensitive and specific detection technologies, which are likely to make accurate diagnoses possible earlier and earlier in the disease process. It is therefore likely that this traditional dichotomy between risk stratification and diagnosis in the early preclinical stages of disease will eventually dissolve. Since there can be no logical cut-off between the clinical accuracy needed for a screening test in a screening programme and that expected of a diagnostic test (and in reality, both may be imperfect), the requirement for risk stratification is one of feasibility and not a conceptual prerequisite for screening. The conceptualisation of risk stratification as a fundamental aspect of screening is, in our view, an artefact largely due to the current lack of highly accurate molecular biomarkers. This situation is now beginning to change, because of scientific and technological advances. In contrast, the presence or absence of symptoms experienced by the individual is likely to remain unchanged by advancing science.

## (3) Offered

Finally, the third criterion – requiring that the test be offered to the patient rather than being implicitly sought by the patient – relates to the ethical burden placed upon the physician or other health care provider offering, promoting or performing the test. We believe that this criterion lies at the heart

of what distinguishes a diagnostic from a screening test, and thus places a high moral burden on respecting individual autonomy.

The ethical standards required when proactively encouraging an otherwise healthy individual to have a medical test are clearly significantly higher than those involved when patients themselves seek medical help. Indeed, the essence of an opportunistic screening test is that the test is unrelated to the symptoms presented by the patient, but is performed on the patient by their physician. Although the increased emphasis on ethical standards is partially related to the first criterion – the lack of symptoms and the predictive value of the test itself – it also relates crucially to the moral responsibility of imposing an uninvited and potentially unwanted medical test upon a member of the public. While seeking informed consent before testing is an absolute ethical requirement, it does not absolve the physician or health care system of its responsibility to offer medically useful screening, where the benefits have been shown to outweigh the harms. The decision to medicalise an otherwise healthy individual (with respect to the disease to be screened for) must be carefully considered[18,19]. The desire of medical professionals to prevent disease in their patients, whilst laudable, is insufficient to proceed with opportunistic screening without a full discussion about the evidence of benefits and risks, and without assurance that the patient is making an informed choice in the context of their personal preferences and the available evidence.

The recent proliferation of direct-to-consumer (DTC) tests has blurred this distinction somewhat, by allowing asymptomatic individuals to autonomously demand genetic and other health-related screening tests (irrespective of whether they are available as part of a screening programme). It is an

arguable point, but we suggest that in seeking such services, the client themselves has taken on a certain responsibility. The commercial test provider is not entirely absolved from ensuring that the risk-benefit ratio of the tests they provide are in the client's interests, but their obligations are perhaps not as high as when a healthcare provider offers a screening test, unsolicited, to the individual.

## CONCLUSION

Given that it is now relatively easy (from a technological perspective at least) to offer genomic screening at the same time as diagnostic genome sequencing, is it still worth making a distinction between screening and clinical testing? We suggest that it is, due to the differing burden or responsibility placed upon the physician and health care system in each scenario. Screening – whether opportunistic or invitational – requires higher standards for two separate but related reasons: first, because screening tests are performed in asymptomatic individuals, where the predictive value and utility of the test is likely to be much lower; and second, because screening tests are generally offered and promoted to individuals, rather than sought by patients who request medical help, thus placing a greater ethical burden on those who initiate the test to ensure that the benefits outweigh the harms. Ethical considerations dictate that separate consent is required over and above that given for the diagnosis and management of the presenting complaint whenever a physician considers opportunistic screening.

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