

IVD Regulation: problems still not solved

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“Future health services will not revolve around consultants in hospitals. Instead, they will facilitate the active involvement of users themselves in providing their own care, drawing on a detailed understanding of a personalised risk profile, working with nurses, pharmacists, nutritionists, fitness experts and other advisers more often than with the specialist doctors of today”. Lord Darzi, 2013.¹

There is currently a major commercial push to use computer algorithms to make predictions of people’s risk of common diseases such as cancers, heart disease, type II diabetes, Alzheimer’s Disease and psychiatric disorders. These risk predictions will be based on information in people’s electronic medical records combined with their genetic make-up. A major rationale behind this approach is to expand the market for medication and other products (health scans, functional foods, supplements etc.) to people who have no symptoms of disease. Earlier treatment of more people (because the “at risk” group is always significantly larger than the number of people who actually develop a disease) has the potential to significantly expand the market for medication and other health products such as functional foods. Although the claimed objective is to “predict and prevent” disease, a major potential downside is the over-treatment of people who would never have developed the predicted disease. People told they are at low risk of a condition might also fail to take important steps to improve their lifestyle.

Currently, most genetic tests look for rare mutations which occur in relatively small numbers of patients, but in future genetic tests may include whole genomes (a person’s entire genetic make-up); or genotyping using hundreds or thousands of SNPs (“snips” or Single Nucleotide Polymorphisms). SNPs are single chemical letters in a person’s DNA which differ between individuals. Advocates of this approach argue that the focus of genetic testing should shift from diagnosing symptoms in children with rare genetic disorders to predicting risk of disease in healthy people. Some believe that every baby will have its whole genome sequenced at birth once this becomes affordable.

The pharmaceutical industry, private healthcare industry, food industry and computer industries (including web-based companies such as Google) see this as an opportunity to massively expand the market for healthcare products (from medicines to functional foods) to be sold to healthy people, based on predictions of their risk of future illness. These predictions may be sold online, or fed back via decision-support systems (using computer algorithms) used by doctors. The leading direct-to-consumer gene testing company marketing online is currently 23andMe, a US-based company run by Anne Wojcicki, wife of Google co-founder Sergei Brin, and partly funded by Google.

To date, sales of genetic tests have been controversial for several different reasons. Firstly, investigations (including by the US Government Accountability Office (GAO);^{2,3} academic researchers⁴; and NGOs⁵) have uncovered numerous examples where false or misleading claims have been made about genetic risk, in some cases accompanied by incorrect health advice or attempts to market products (usually supplements). These problems often arise due to the inclusion of SNPs that are not actually related to the risk of the disease (usually due to the large number of false statistical associations in the published scientific literature). Secondly, there is no definitive method to interpret an individual’s genetic risk from pieces of information about the risk associated with different SNPs in different studies: these risks may depend on the context (both environmental and biological) and may combine in complex ways, which are not yet fully understood and may not always be predictable.⁶ These two problems mean that different companies may give very different

interpretations of a person's risk based on the same DNA.⁷ Thirdly, there is growing evidence that the predictive value of genetic information for most diseases in most people is (and will remain) rather poor (even when more research is done), meaning that many genetic tests do not provide useful information for a person's care (and the usefulness is often exaggerated in marketing materials).⁸ This is also the case for many (but not all) genetic tests which aim to predict drug response (pharmacogenetic tests).⁹ Finally, because rare mutations can sometimes have unexpected serious consequences (even though most tests have poor predictive value) there is the potential for nasty surprises which people may not be prepared for unless they have pre-test counselling to explain the pros and cons.¹⁰

The potential for more widespread use of genetic testing by healthcare systems in the future also raises major concerns about data protection and fundamental rights (including privacy) because genotypes including large numbers of SNPs and/or whole genomes act as biometric identifiers for individuals and their relatives.

In the case of genetic tests, analytical validity concerns whether or not the method used correctly identifies the genotype (i.e. the string of chemical letters making up a person's DNA). Clinical validity concerns whether or a particular genotype is associated with an increased or decreased risk of a particular disease, and the predictive value of the test or computer algorithm (which may be based on many different SNPs and perhaps other variables as well). This affects the numbers of "false positives" (people who are told they are at high risk of a disease which they never develop) and "false negatives" (people told they are low risk of a disease which they do develop). Clinical utility concerns whether benefits outweigh harms when the test is used for a particular purpose in clinical practice. This depends on the stated purpose. For example, a test to diagnose a rare genetic disease may not actually improve health outcomes but might still be beneficial for a family to understand the cause of certain symptoms; a test to predict a late-onset disease might also be useful for individuals and their families to inform decisions, even if there is no treatment. However, if a test is to be used to target treatments or lifestyle advice (as its stated purpose) it is important to know whether using the test to target the recommended intervention(s) actually improves health outcomes (for example, by reducing the incidence of a disease or adverse drug reaction).

Until now, genetic tests have been poorly covered by EU regulation (the IVD Directive), partly because they were classed as low risk (and hence left to be in effect self-regulated) and partly because the IVD Directive focused on the technical properties of the test (known as "analytical validity") and did not require all the necessary evidence about its predictive value (or "clinical validity") or usefulness for health ("clinical utility") to be provided. It is important to note any that requirements for oversight by doctors (whether this is included in the Regulation or not) will not remove the need for regulatory assessment of complex genetic tests and predictive software, as many thousands of scientific papers may be relevant to a given risk assessment and statistical studies are often contradictory or variable in quality. Doctors and even academic experts are unlikely to have the time, resources or expertise to disentangle this complex and often contradictory information.

The new IVD Regulation has an improved scope and requirements for technical documentation. However, there remains (i) no pre-market review or publication of the manufacturer's data on clinical validity; (ii) no requirement to provide, review or publish data on clinical utility. These major omissions render the proposal worse than useless as they merely give the appearance of regulation (via the CE mark), which is almost entirely superficial.

Currently, the Regulation does not meet the claims made in the Memorandum that the proposal seeks to ensure a high level of human health protection (Article 35) and consumer protection (Article 38) in line with the Charter of Fundamental Rights of the EU.

In the USA, the FDA has announced it will undertake pre-market assessments of genetic tests^{11,12} and it is therefore a major concern that the EU appears to be about to set much lower standards. This inevitably raises suspicions that commercial lobbyists may be looking to the EU-US Free Trade Agreement (which will cover diagnostics) to seek to undermine regulation of genetic tests by the FDA. This can only have negative outcomes for health inside and outside the EU. This approach risks removing incentives for those manufacturers wishing to set high standards by providing meaningful interpretations, in favour of allowing poor quality misleading tests access to the market. In the longer term, this approach could stifle innovation as medical professionals and the general public are likely to lose trust in the information provided to them.

SCOPE

The draft IVD Regulation now covers medical devices, including software, used for the purpose of providing information concerning the predisposition to a medical condition or disease; or to predict treatment response or reactions (Article 2(2)). Human genetic tests are classified as Class C, according to Annex VII (classification is required by Article 39). Companion diagnostics (which include pharmacogenetic/pharmacogenomic tests i.e. genetic tests for drug response) are also Class C.

This is a significant improvement on the previous IVD Directive because predictive tests (including software combining risks of multiple genes and other factors) are now clearly within the scope, and including genetic tests as Class C means they are amongst higher risk devices. However, there is a loophole in Preamble point (10), which excludes software intended for “well-being” applications. “Well-being” is not defined in the Regulation and has sometimes been interpreted by commercial companies to cover most areas of predictive medicine, including genetic tests combined with lifestyle advice or recommendations to take preventive medicines or supplements. There are also some small inconsistencies in definitions elsewhere in the Regulation.

Recommendation: The phrase “software intended for well-being applications” should be deleted from the Preamble point (10), page 12.

The definition of an in vitro device Article 2(1) needs to include "prediction" as well as diagnosis etc. of disease. Annex VII 2.3 Rule 3(f) also needs to include in (ii) "disease staging or prognosis" and in (iii) "diagnosis or prognosis".

REQUIREMENTS

Analytical validity

Requirements for analytical validity are included in the performance requirements for devices listed in the general requirements (Article 47(3); Annex I, 6.1). Accuracy, precision and stability of measurements are required by Annex I, 11.1, and analytical performance characteristics must be included in the instructions for use (Annex I, 17.3.1) and technical documentation (Annex II, 6.1). The manufacturer is required to adopt a quality management system, audited by the notified body (Annex VIII, Chapter I).

Clinical validity

Requirements for clinical validity are included in the general requirements, Annex I, 6.1b (diagnostic sensitivity, diagnostic specificity, positive and negative predictive value, likelihood ratio, expected values in normal or affected populations). However, Article 47(4) allows performance requirements to be based on analytical performance evaluation alone, provided “adequate justification for any

such exception” is given. No rationale for the inclusion of this exception is given, nor any process for challenging such decisions.

For genetic and genomic tests, algorithms are likely to combine the predicted effects of multiple variants to predict disease risk of drug response. Annex I 13.1 requires software verification and validation and the description of the data interpretation methodology (i.e. algorithm) must be included in the technical information (Annex II, 3.1(d)), as must the results of verification and validation testing (Annex II, 6), including evidence of the validation of the software (Annex II, 6.4).

Instructions for use must include inter alia, the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate and where applicable, the testing population, and, where relevant, clinical performance characteristics, such as diagnostic sensitivity and diagnostic specificity (Annex1, 17.3.1).

Where applicable, the technical documentation shall contain data on the clinical performance of the device and the clinical evidence report referred to in Section 3 of Annex XII shall be included and/or fully referenced (Article 47(3) and (5); Annex II, 6.2).

Recommendations:

The exception in Article 47(4) which allows performance requirements based on analytical performance alone appears arbitrary and should be deleted.

Clinical utility

No requirements for clinical utility are included in the Regulation.

In 2003, the Institute for Prospective Technological Studies (IPTS) of the EC Joint Research Centre (JRC) warned that *“the problem of increasing number of tests that are performed with a dubious clinical utility should be considered as they might become in the near future an unnecessary burden for health care systems”* and stated: *“As there are potential harms attached to genetic testing, tests should only be considered if benefits clearly outweigh harm”*.¹³ In 2004, the report of the EC’s expert group on genetic testing¹⁴ stated: *“Proof of clinical utility and subsequent validation of all genetic tests are prerequisites before their implementation into clinical routine”*.

The Council of Europe’s Additional Protocol on Human Rights and Biomedicine, Concerning Genetic Testing for Health Purposes (Article 6) states: *“Clinical utility of a genetic test shall be an essential criterion for deciding to offer this test to a person or a group of persons”*¹⁵.

OECD guidelines for quality assurance in molecular genetic testing¹⁶ state: *“Laboratories should make available to service users current evidence concerning the clinical validity and utility of the tests they offer”* (B.vi).

The US Secretary’s Advisory Committee on Genetics Health and Society (SACGHS) report defines the clinical utility for clinical decision-making as the balance between the benefits and harms of testing and ensuing follow-up evaluation, treatment or prevention (page 117).¹⁷ Clinical utility must be evaluated within a specific context and utility may vary, depending on the context and available alternatives. The assessment of clinical utility presumes that a minimal threshold of analytical and clinical validity has been established. The report notes that *“tests for which clinical utility is known but where harms exceed benefits should not generally be used...”* and that, when there is inadequate information: *“Genetic tests without proven clinical utility could divert clinical management away from effective strategies to those that are uncertain (or even harmful)”* (page 137).

Recommendation: Manufacturers should be required to provide data on clinical utility where appropriate i.e. when clinical utility requirements relate to the stated purpose of the test. It is particularly important that manufacturers are required to provide data on clinical utility for companion diagnostics i.e. when an intervention is intended to be tailored to the outcome of the test. Failure to include clinical utility requirements means that a manufacturer could claim that a certain test outcome required certain actions to be taken by a patient or their clinician when in fact those actions might worsen rather than improve health outcomes. Failure to request data on clinical utility puts medical professionals and regulators in a difficult position if they are unable to verify claims made by manufacturers.

ASSESSMENT PROCESS AND NOTIFIED BODIES

Although the scope and evidence requirements (with the exception of clinical validity) have been significantly improved compared to the IVD Directive, the proposed mechanism for regulatory oversight is extremely poor.

The conformity assessment process as described in Article 40 (using Annex VIII or, if manufacturers choose it, Annex IX and X) does not include any scrutiny of the clinical performance data or most of the general requirements and technical documentation (including, for example, the predictive value of the tests). The notified bodies can ask to see this information and review it if they wish, but they aren't required to even look at it (or to publish it). This problem also applies to the EMA's proposed role in conformity assessment for companion diagnostics (Article 40(2)) i.e. the EMA has a narrow role which may cover only checking the Quality Assurance (QA) process (i.e. analytical validity).

In the case of genetic tests, this means the notified bodies can award the CE mark after checking only whether the correct DNA sequence has been identified: they are not required to check the interpretation of what this sequence means for a person's health or future treatment. This renders the CE mark effectively meaningless to the end user (the clinician and the patient) because it fails to protect them from misleading claims.

National authorities are responsible for notified bodies (Article 26), which carry out the third party conformity assessment tasks required by the Regulation. Requirements for notified bodies are in Annex VI. Manufacturers can terminate a contract with a notified body and contract with a new one (Article 44). This risks a "race to the bottom" in terms of regulatory oversight.

Article 42 allows some scrutiny of certain conformity assessments by the expert body (MDCG). The MDCG can request copies of summaries of the preliminary conformity assessment from notified bodies for class D devices, provided there is a scientifically valid health reason, and submit comments and/or request samples or on-site visits. For human genetic tests (class C devices), Article 42(5) may allow some scrutiny by the MDCG if such tests are regarded as novel, or for other reasons including significant discrepancies in the conformity assessments carried out by different notified bodies on substantially similar devices; or public health concerns.

Previous investigations have found major discrepancies between interpretation of genetic test results by different providers (for example, based on the same DNA, different companies may tell the same person that they are at low, high, or medium genetic risk of heart disease). This problem will not be addressed unless: (i) pre-market assessment of clinical validity (and, where appropriate, clinical utility) is included as a regulatory requirement for all tests; (ii) there is a mechanism which ensures consistency of assessment standards across the EU.

Recommendations:

Assessment of the general requirements, technical documentation and clinical performance data, covering analytical validity and, where appropriate, clinical utility must be included as a requirement in the scope of the pre-market conformity assessments.

To ensure consistency, it would be preferable to not use notified bodies at all and require pre-market assessment of all tests by EMA. However, some kind of compromise position might also be reached where EMA has oversight of the notified bodies and conducts regular assessments of consistency and completeness of the conformity assessments. This must include clinical validity and, where appropriate, clinical utility, not merely analytical validity and quality assurance.

TRANSPARENCY AND PUBLIC INFORMATION

To date, misleading and false claims about genetic test results have been widely marketed. These claims have been uncovered by investigations by NGOs, academics and the US Government Accountability Office (GAO), as cited above. However, the failure to include any transparency requirements in the Regulation means that it will not be possible for any of these agencies, or for clinicians or patients to check any claims made by manufacturers in future. This is because most of the information supplied to the notified bodies will not be made publicly available. This allows manufacturers to use “black box” computer algorithms to calculate individual risks without publishing any information about which genetic variants and other data is included, or what assumptions they are using to make the calculations, or any evidence that these predictions have been validated to see if they are in any way realistic or reproducible. This could lead to significant harm to health as a result of incorrect interpretations.

Under the Regulation as written, even clinicians will not necessarily be able to see most of the evidence which the manufacturer submits to support its claims. Further, manufacturers will continue to be able to make advertising claims which are not consistent with the evidence. This contravenes the OECD Guidelines cited above, which state:

- Advertising, promotional and technical claims for molecular genetic tests and devices should accurately describe the characteristics and limitations of the tests offered (A.9).
- Laboratories should make available information on the analytical and clinical validity of tests (A.ii).
- Laboratories should make available to service users current evidence concerning the clinical validity and utility of the tests they offer (B.vi).
- The interpretation of molecular genetic test results should be appropriate to the individual patient and should be based on objective evidence (D.4).
- Reports should be timely, accurate, concise, comprehensive, and communicate all essential information to enable effective decision-making by patients and healthcare professionals (D.ii).

Recommendations:

The General Requirements in Annex II should have an additional Section 7: PUBLIC AND PROMOTIONAL MATERIAL. This should make the technical documentation and clinical evidence submitted by manufacturers to notified bodies publicly available (so clinicians and users can actually see it); ban DTC advertising of those tests that are not allowed to be sold DTC; and require all advertising and promotional material (including online) to accurately describe the characteristics and limitations of the tests offered.

Part A of Annex V specifies what will be included in the electronic system which is accessible to the public (Article 23(6)): this needs amending to include the full technical documentation and the clinical performance report. This allows clinicians, users and others to check the claims. Article 23(1) which refers to this information should be amended so the first sentence adds as a purpose "*and to ensure transparency and safe and effective use by making available to users current*

evidence concerning the clinical validity and, where applicable, utility of the device". Parts of the Regulation which refer to confidentiality may need amending to make clear that the final documentation should not be confidential. (Data protection requirements do, of course, need to be kept).

There should be an explicit requirement to create a register for genetic tests (Article 79).

Complaints are mentioned in Article 65(1) but no mechanism is specified to deal with complaints or input from health professionals, experts, users or members of the public, except under the vigilance system for serious incidents. There should be a process to report other problems and developments such as new performance data, misleading advertising or incomplete instructions (i.e. to report any 'device deficiency' as defined in Article 1(48), or any failure to meet the regulatory requirements). This should be a standard part of the post-market monitoring process. Article 4(5) states that Member States may require that the health institutions submit to the competent authority a list of devices used in a single health institution, which are exempt from the full requirements of the Regulation. It should be a requirement to provide this list.

DATA PROTECTION, PRIVACY RIGHTS AND INFORMED CONSENT

The importance of protecting personal data is rightly recognised in the Preamble point (31) page 16 and point (44), page 17, which requires that no personal data of subjects participating in clinical performance studies is recorded in the proposed EU-level electronic system (see also Article 22(8)). Article 81 requires Member States and the Commission to meet data protection requirements. Annex XIII requires a description of the arrangements to comply with protection and confidentiality of personal data during clinical performance studies.

The importance of the Declaration of Helsinki and the need to comply with ethical and good practice guidelines for clinical investigations is recognised in the Preamble point (43), page 17 and in Annex XII 2.2. Article 48 requires that the rights, safety and well-being of the subjects participating in clinical performance studies are protected. Where the conduct of the study, including specimen collection, involves invasive procedures or other risks for the subjects of the studies, the requirements set out in Articles 49 to 58 and in Annex XIII shall also apply. This sets up a system of applications for trials, registration of them, sharing of information, and recording and reporting of adverse events and device deficiencies that might lead to adverse events (Article 57(1) and (2)). Annex XIII 4.4 requires information on documents and procedures used to obtain informed consent.

The draft Rapporteur's report introduces further amendments regarding informed consent.¹⁸ However, neither the draft Regulation nor the Rapporteur's report makes clear that risks for the subjects of studies may include significant privacy risks (not merely risks of interventions such as needles and drugs). This is particularly important in the case of stored genetic and genomic information as multiple SNPs or whole genomes have sufficient discriminatory power to identify individuals and their relatives (including non-paternity).

Biometric systems use a certain unique property of an individual for identification and/or authentication, such as DNA. Unlike stored data, a biometric cannot be altered because it is linked to a person's body. The EU's Article 29 Data Protection Working Group has warned that biometrics allow for automated tracking, tracing or profiling of persons and as such their potential impact on the privacy and the right to data protection of individuals is high.¹⁹ The Working Group states that a prerequisite to using biometrics is a clear definition of the purpose for which the biometric data are collected and processed, taking into account the risks for the protection of fundamental rights and freedoms of individuals, and: *"It must be clear that such consent cannot be obtained freely through mandatory acceptance of general terms and conditions, or through opt-out possibilities"*. Further, in a unanimous judgment by the Grand Chamber in December 2008 in the case of *S. and Marper v. the UK*, the European Court of Human Rights found that the indefinite retention of two innocent

persons' biological samples, forensic DNA profiles and fingerprints "constitutes a disproportionate interference with the applicants' right to respect for private life and cannot be regarded as necessary in a democratic society". This suggests that any attempt to retain biometric data (such as whole genomes or genotypes) without consent for health or research purposes is also likely to be in breach of the Convention.

Apart from any counselling requirements, the proposed amendments by the Rapporteur regarding medical supervision of genetic tests play an important role in ensuring the people being tested have given their fully informed consent, or (for children or others lacking capacity) that consent has been provided by the relevant adult parents or carers. When tests are sold on line, the origin of samples (particularly saliva samples, which can be obtained surreptitiously) may be impossible to verify.

Recommendation

All references in the Regulation (or any subsequent amendments) to research involving risks should state explicitly that risks may include risks to privacy.

Face-to-face contact with a medical professional is essential to ensure requirements for fully informed consent are properly fulfilled for genetic tests, because samples of saliva can easily be obtained surreptitiously.

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