

Official response of the EuroGentest Network of Excellence in Genetic Testing

to the

Public consultation on the revision of Directive 98/79/ec of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices

Introduction

We are grateful to the Commission for providing this opportunity to contribute to the revision of Directive 98/79/EC on *in vitro* diagnostic medical devices.

EuroGentest is a Network of Excellence promoting harmonization and quality in genetic testing, established in 2005 under the EU 6th Framework. EuroGentest represents many hundreds of laboratories and genetics centres across all EU member states and beyond.

Quality is at the heart of EuroGentest's mission. EuroGentest maintains that only high quality, clinically and analytically valid diagnostic tests should be performed in clinical laboratories. EuroGentest promotes accreditation to appropriate international standards such as EN ISO 15189:2007 "*Medical laboratories — Particular requirements for quality and competence*". EuroGentest also maintains that accreditation, regular participation in external quality assessment schemes (which are themselves accredited) and adherence to professional guidelines such as those produced by the European Molecular Genetics Quality Network, ensures the availability of safe, effective, appropriate, and patient-oriented genetic testing. Furthermore, the OECD has issued *Guidelines for Quality Assurance in Molecular Genetic Testing*, which state "All molecular genetic testing results for clinical care purposes should be reported by competent laboratories, as established by accreditation or other equivalent recognition". Our responses set out below are drafted in this context.

EuroGentest maintains that tests developed and validated "in-house" by expert laboratories are an essential and central component of medical practice. Laboratory professionals who perform such tests have, and must continue to have, vital roles in working with clinicians to improve patient management. In-house tests have contributed to major advancements in the diagnosis and management of inherited diseases, as well as a wide range of cancers. Additionally, in-house genetic tests are used to identify suitable bone marrow donors, and allow doctors to monitor the disease course in transplant recipients. These are but a few examples of the hundreds of in-house tests available. Without such tests, the practice of medicine that we know today would be severely reduced in scope. EuroGentest is in favour of the regulation of all tests, whether in-house or commercial, but there are different regulatory pathways available to achieve the common aims of test quality and patient safety.

We wish to emphasise that we are not promoting special treatment for genetic testing in any revised Directive; many of the points we make could apply to any kind of specialist testing, and many tests which have a predictive value are not genetic tests. The revised Directive should be flexible enough to cover all types of test in an even-handed way, in the best interest of patients.

Question 1: – Would you consider the adoption of a **risk-based classification** for *in vitro* diagnostic medical devices as an improvement of the current European regulatory framework?

We believe that a risk-based classification system would be preferable to the current list-based system because it would be more *coherent* and *consistent* and would provide a greater level of *protection for public health* by subjecting a broader range of tests to independent pre-market evaluation.

A major problem with the current approach in the Directive is a lack of consistency. The Directive sets out three criteria which would determine whether a test should be added to Annex II:

“(i) whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action, and

(ii) whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false positive or false negative results, and

(iii) whether the involvement of a notified body would be conducive to establishing the conformity of the device.”

But whilst there is a set of criteria, there appears to be little consistency as regards what is currently classified as moderate-risk and what is low-risk. Thus Chlamydia tests are in Annex II, List B, but no other tests for sexually transmitted diseases; PSA is also on List B, but no other cancer test; there is one heritable disorder, PKU, but no others. Furthermore, experience has shown that a list-based approach to classification is not an effective mechanism for risk classification of novel tests. The automatic assumption is that all new tests are low risk and this creates further inconsistency. For instance, Gen-Probe’s PCA3 test quantifies the PCA3 mRNA in a patient’s urine sample as a marker for prostate cancer and thus performs exactly the same clinical function as the PSA test, yet it has not been added to Annex II, List B.

An international comparison of device regulations shows that the European approach to risk classification for genetic tests is uniquely liberal. In the United States, Canada and Australia genetic tests which fall within the medical device regulations are all treated as moderate to high risk – and so are generally subject to pre-market review (in Australia some genetic tests are Class II and exempt from pre-market review). There are a number of reasons for considering that many genetic tests are moderate- to high-risk. These factors may be divided between those which relate to the intended clinical use of the test and those which relate to other factors:

Intended use

1. They are often stand-alone, with no confirmatory test available.
2. They are used for relatively serious clinical purposes, such as pre-implantation genetic diagnosis and selecting treatments (pharmacogenetics).
3. They may have serious psychological impact (e.g. Huntington Disease).

Other factors

4. Many new tests are highly complex involving multiple alleles or multiple genes, making interpretation more difficult, interpretation may depend on an algorithm which may be proprietary.
5. If it is a test which is performed in a single reference laboratory, then it will not undergo informal peer-review by the pathology community (an issue which may also relate to the use of proprietary interpretative algorithms).
6. The pace of discovery in genomic science means that there is a proliferation of new testing platforms and new biomarkers with potential clinical application. New genetic tests carry the risks associated with all novel devices – unproven performance in the field and lack of familiarity on the part of users.
7. An increasing number of genetic tests are available direct-to-consumer (DTC).

The GHTF model

By contrast the risk classification schema developed by the Global Harmonisation Task Force is both more comprehensive and more consistent.¹ Largely modelled on the Australian system (itself a refinement of Canada's model) it is a four-class system running from high- to low-risk. The risk of a test is assessed using a number of criteria, such as the intended use/indications for use, the skill of the user, the degree of reliance placed on the test result, and the potential impact on public health and the individual patient. Examples of existing tests have been assessed according to these criteria and placed in one of four categories and this guides manufacturers in how to classify their new tests.

The GHTF model places all genetic tests into the moderate-to-high risk (Class C) category. The original GHTF consultation document placed some genetic tests in class B and some into Class C. It is clearly the case that some genetic tests pose greater risks than others, but when all risk factors are taken into account, there is good reason to treat most genetic tests as Class C. There is an increasing availability of tests predicting susceptibility to common diseases such as stroke and diabetes. For the most part such tests predict relatively minor modifications of an individual's risk and some believe that such susceptibility tests should *not* be treated with as strict regulatory scrutiny as genetic tests which provide information with much greater clinical impact, such as diagnosis of Huntington Disease or Cystic Fibrosis. However, risk classification is based on *probability* as well as *severity* of harm (see GHTF definitions, section 4), and there is good reason to consider that probability of harm is greater with this class of tests, largely because of the continued uncertainty of the science, the highly polygenic nature of most common disease, the failure to discover as yet more than a small portion of what is estimated to be the heritable component of common diseases and the speed with which genetic discoveries are being commercialised (often as direct-to-consumer tests, see below). Moreover, there is in some cases the possibility of severe harm. For instance, there is anecdotal evidence of people considering prophylactic surgery in the wake of being told they are at increased risk of cancer, even when the increased risk is relatively minor.² For these reasons it seems reasonable to require susceptibility tests to be subject to pre-market review of the sort applied to tests at a class C level.

Novelty as a risk factor

It should be clear from the preceding argument that the novelty of the biomarkers being used in susceptibility testing is a major factor in the risks which they pose. Here there is a problem: the GHTF model does not treat novelty as a risk factor. This is contrast to the US regulatory system, in which novel tests are automatically classified as high-risk (Class III in the US system) and subject to the most rigorous conformity assessment route (in practice, classification can be appealed, and generally most new tests are reclassified as Class II, and subject to a less rigorous pre-market review (*de novo* 510K, roughly equivalent to Class C conformity assessment route in the GHTF model)). Experience would suggest that lack of familiarity with a new test - whether it is the testing platform, the biomarker/s, the interpretative algorithm, or any combination of these three

- can lead to errors. The true performance of a test, both its analytic and clinical validity, is not known until the test has been in routine clinical practice for some time. Furthermore, tests generally perform less well in routine use than they do in clinical investigations. For these reasons, novel tests are more likely to lead to incorrect results and so novelty should be formally acknowledged as a risk factor.

In this regard, it should be noted that industry supports the use of novelty as one of the primary criterion for risk classification, at least in the US. The US industry body AdvaMed has recently argued that FDA should adopt a revised approach to risk classification which focuses on novelty and complexity, as well as intended clinical use:

Regulatory requirements should be determined based on the management of the risk associated primarily with the clinical intended use(s) of the test, along with consideration of novelty of the analyte, technology or test platform, and site of service/experience of the operator.³

There is one further requirement for the proposed system to operate effectively: a mechanism to decide on the classification for those tests whose status may be ambiguous. Clearly judgements will have to be made about the intended use of some tests, e.g. those tests in Rule Three of the GHTF model. This rule assigns to Class C those tests which are intended to be used “in screening for selection of patients for selective therapy and management, or for or for disease staging, or in the diagnosis of cancer. Example: personalized medicine.” However, this is qualified to exclude those tests “where the therapy decision would usually be made only after further investigation and those used for monitoring would fall into class B.” Such distinctions may: 1) make sense in principle but they may be difficult to implement in practice. Furthermore, there are some categories of tests in development which might raise concern but are not discussed within the GHTF model. For instance, there is a great deal of interest in using new genomic/proteomic biomarkers for early identification of Alzheimer’s Disease. Such applications are fraught with potential dangers, in part because of the well-established problems associated with the trade-off between clinical sensitivity and clinical specificity in screening tests, but also because of the difficulties of clinical validation in a condition like dementia which contains a broad spectrum of phenotypic variation. The new risk classification schema should be informed by a horizon-scanning exercise to identify the range of novel tests being developed which may not have been considered during the development of the GHTF model. Looking to the future, the classification of novel and ambiguous tests will need an EU-level body able to respond promptly, as decisions made by notified bodies or competent authorities would run the risk of creating inconsistency.

Ambiguity in risk classification may offer significant scope for creative construction of intended uses by manufacturers and discrepancies between the stated intended use and the use promoted in practice, both in relation to Rule three, Class C tests and new screening tests (for instance, in the USA the PSA test was approved for monitoring patients diagnosed with prostate cancer but promoted for screening use). There is an inherent danger in applying a test to populations or purposes for which no good clinical evidence exists, and where the intended use has not been independently evaluated. Regulatory strategies to deal with this include requiring manufacturers to include prominent warnings about the lack of data/approval for off-label uses on their label/instructions or requiring them to provide evidence on the most common clinical applications. More rigorous surveillance of postmarket promotional activity and enforcement against those companies promoting off-label uses is required. Despite the greater importance placed on postmarketing surveillance, in both the US and Europe there is little evidence of systematic and rigorous regulatory activity to deal with this problem.

– Are you aware of any **consequences** for the protection of **public health**?

As noted above we believe that a more consistent and comprehensive approach to risk classification would provide greater protection of public health by ensuring that most moderate/high-risk tests are subject to some level of pre-market evaluation. We believe that this can ensure that companies are properly restricted in the types of claims which they make for their tests, helping to ensure truth-in-labelling and truthful promotion, and that, tied to the development of standards (see below) it can promote a more rigorous approach to clinical validation of new tests.

– Can you provide **economic data** linked to a change-over to this GHTF classification system?

Regarding costs or savings resulting from this change, we have no data to provide. However, we would note that adoption of the GHTF model would bring Europe more closely in line with the US and Canadian systems and the proposed new model for Australia. Such international harmonisation is of benefit to industry as it creates a more consistent regulatory landscape. Furthermore, bringing more tests into the moderate-high risk category, and subjecting them in effect to the equivalent of the FDA's 510k review should not pose an undue burden to industry. Industry is well-represented on the GHTF and have had ample opportunity to help shape the GHTF approach.

Question 2:

In the context of a possible adoption of a **risk-based classification** according to the **GHTF model** (see above 1.) do you see a need for amending the current conformity assessment procedures for *in vitro* diagnostic medical devices?

Yes.

Question 3:

If yes, in your view which are the **conformity assessment procedures** that should be **deleted or amended** and **why**?

Since at the moment there are only three conformity assessment procedures (CAP) then a four-class system would require, as a minimum, adoption of a further CAP. Consideration should be given to adoption of the GHTF conformity assessment model and the GHTF's model, since this was developed in parallel with the GHTF risk classification schema. However, the GHTF model places insufficient emphasis on data collection in the postmarket phase. A focus on only adverse event data collection will not capture the wider data which may generally become available once a new test is on the market. As already discussed (novelty as a risk factor), test performance in clinical practice is generally different to test performance during product development. Manufacturers should be obliged to have a system for collection of such data and for updating of the technical documentation, instructions for use, product labelling etc., where appropriate, in the light of new data.

Question 4:

Would you consider appropriate to **require for all IVDs**, except for those in class A of the GHTF classification, at least the **pre-market control** of the manufacturer's **quality management system** by a third party as laid down in GHTF/SG1/N046:2008?

See Q3 above.

Question 5:

In the context of the "**batch release verification**", do you consider that a **control of each batch** of manufactured **high-risk IVDs** should be required prior to their placing on the market?

Yes, it seems self-evident to us that each batch of IVDs should be verified to perform according to the manufacturer's claims before release onto the market. Such a verification would not be overly burdensome; it could be restricted to a demonstration that the reagents perform as expected when tested on suitable reference materials.

If yes, what would be the **purpose of batch release verification** and **which IVDs** should be subject to such a control?

The purpose would be to demonstrate that this batch of reagents perform according to the manufacturer's claims. All IVDs should be subject to such a control.

If yes, how (testing, verification of the results of the tests) and by whom (manufacturer under the control of notified bodies, notified bodies, independent laboratories) these controls should be performed?

The verification should be performed by the manufacturer and the records of such verification retained for inspection as necessary by Notified Bodies.

Question 6:

Should the use of **Common Technical Specifications (CTS)** be maintained for **high risk IVDs**? Should CTS also be adopted for other IVDs?

The question of CTS is part of a far broader issue relating to the use of standards in the EU regulatory system. To date the only CTS produced have been for Annex II, List A devices and there is in general a lack of harmonised standards for other kinds of tests. Thus to date there have been no guidance documents or other kinds of standards developed for genetic/genomic tests in Europe, an issue which some industry stakeholders have suggested to us was a problem for them and which offers little protection for public health. It also may be helpful if there could be greater international coordination in the development of guidance, as a more consistent approach would lessen the regulatory burden for companies. Amongst medical device regulators, the FDA is the most advanced in its development of guidance on the evaluation of genetic tests. It is not unusual for regulators from other countries to adapt FDA guidance documents and it may be that Europe can learn from the FDA's experience. Whether this absence of standards is dealt with through harmonised specific requirements or another harmonised European standards system is less important than the need to address this gap.

Question 7:

Would it be necessary to maintain the exemption provided for by article 1(5) of Directive 98/79/EC and why?

Yes. We believe that it is essential to maintain the exemption provided for by article 1(5) of Directive 98/79/EC. However, the exemption is currently ill-defined and there would appear to be significant variation between member states in the interpretation of its scope. We believe that the exemption was intended to, and should cover, clinical laboratories which are part of the public healthcare system *and which are accredited to an appropriate international standard such as ISO 15189*.

There are several reasons for this:

1. Rare Disease testing

Tests for rare diseases (conditions affecting not more than 5 in 10,000 persons in the EU) are evidently employed less frequently than tests for more common conditions. Although a few conditions in this category are common enough that commercial production of IVDs for them is viable (e.g. cystic fibrosis), the vast majority of rare disease tests will only ever be available from specialist centres. CE marking of every test offered in such centres is scientifically and financially impractical. It is certainly in the interest of patients to ensure that all such testing is carried out within an appropriate quality framework, but a requirement for CE marking would result in the loss of most rare disease testing. It also needs to be borne in mind, that while genetic diseases may be individually rare, overall they account for a significant burden of disease, of the order of 5% of all medical conditions, and more so amongst patients receiving secondary care: 71% of admissions in one study of paediatric care had a significant genetic component.⁴

2. Customised tests for common genetic diseases

Many inherited disorders are quite common (for example, inherited forms of breast cancer account for 5-10% of all cases), but the underlying mutations are individually rare and may even be confined to a single patient or family. For such diseases, each mutation may require a specially-designed genetic test (and one that may need to be developed urgently, e.g. in a prenatal situation). It is entirely impractical to CE-mark a test that is used for a single family or a very small group of patients.

3. Population-specific tests and test panels

The frequencies of mutations which cause inherited disorders vary dramatically between populations, even within the EU and within individual countries in the EU. A CE-marked assay may be well suited to one population but entirely unsuited to another population or sub-population. Industry will develop test panels suited to the most frequently-tested populations, leaving smaller other populations disadvantaged, unless local specialist laboratories are enabled to develop appropriate in-house panels of tests suited to the population being served.

4. Cytogenetics and other whole-genome testing

Conventional karyotyping involves the culture of cells from the test subject and the examination of fixed metaphase spreads using a microscope. As the appearance of the chromosomes is exquisitely sensitive to the stage of cell division reached at the time the metaphase was fixed, the test and its interpretation is unique for each patient and even for each metaphase. There is no prospect of such a test meeting the requirements for CE-marking (although specialist reagents employed may themselves be considered IVDs). Without an exemption for in-house tests, karyotyping would be illegal. Modern technologies for whole-genome analysis will play an increasing role in replacing karyotyping and broadening the range of testing possible, but karyotyping will play an important role in medicine for many years to come. Furthermore, all of these whole-genome analysis technologies, including karyotyping, share the characteristic that they may produce

results unrelated to the clinical question which prompted the test request, requiring expert interpretation in the context of the patient's phenotype and the inheritance pattern or sporadic nature of the indication for referral. Such testing (and the customized confirmatory testing often required for individual cases) is not amenable to CE-marking and is most appropriately carried out in specialist laboratories accredited to perform and interpret the results of such testing.

5. Seldom-used tests for common analytes

While CE-marked assays will be available for most routine diagnostic tests, particular circumstances, including unexpected results from CE-marked tests, will require the application of less frequently-used tests to confirm or supplement the primary test. Although applied to common conditions, such tests may not be applied with sufficient frequency to create a viable market for a commercial assay. The exemption for in-house tests ensures their availability.

6. Rapid response to changes in test requirements

In recent years we have seen the rapid emergence of global health threats from infectious agents: SARS, Influenza H5N1, H1N1 etc. Such outbreaks require the rapid development and deployment of new assays for detection, monitoring and vaccine development. It would not be possible to implement such testing in the time-scale required if each new assay had to go through the CE marking process.

7. The safety provided by alternatives in test methodology

When a single CE-marked assay (sometimes protected by patent) dominates the market for testing for a particular target or analyte, any systematic deficiency or weakness of that assay may go undiscovered, as alternative methods are not available to confirm the results of the dominant assay. Examples of this have been seen in the external quality assessment schemes run by the European Molecular Genetics Quality Network.

While harmonisation of test standards and comparability of results are very desirable, it is essential that a variety of methods are available and in regular use for each test. Specialist reference laboratories, applying their validated in-house developed tests, play an important role in this regard.

8. Economic risks

If specialist genetic testing within the EU should be restricted because of a requirement for CE marking, then patients and their clinicians would obtain such testing from laboratories outside of the EU.

This poses several additional risks:

- a. tests could be obtained from laboratories operating in less rigorous quality and accreditation environments;
- b. patients and healthcare systems could be liable to higher costs for tests, because of reduced competition and availability – a “sellers market”;
- c. the loss of technical, scientific and medical jobs within the EU associated with genetics laboratories;
- d. the loss of considerable income to the EU, because of the loss to the worldwide community of tests currently only available in the EU;
- e. the loss of scientific prestige, influence and resources from the EU.

The perceived risks posed by in-house tests exempt from the Directive are theoretical, and can be mitigated by implementation of appropriate quality assurance systems which include assay

validation and laboratory accreditation based on EN ISO 15189:2007. Accreditation to this standard, or equivalent, should be a condition of exemption (see Item 4 below). Abolition of the exemption, resulting in the non-availability of specialist testing, would certainly be harmful to patients; it is also arguably discriminatory against those individuals who warrant having such testing.

Question 8:

If the exemption provided for by article 1(5) of Directive 98/79/EC should be clarified or limited, which of the following items you would consider as appropriate in order to clarify the scope of this exemption and ensure a high level of safety:

Item 1:

Better define the concepts of "in-house test", "health institution", "premises of a manufacture or premises in the immediate vicinity". Could you suggest an appropriate definition for these terms?

Response:

Yes, it will be essential to provide clear definitions, as these will determine the scope of the exemption.

When formulating new definitions, it is essential to have a specific objective or objectives in mind, so one must first seek answers to some questions on policy:

What is the purpose of the exemption?

This question is, of course, answered by all the arguments made in favour of retaining the exemption, in the answer to question 7.

The exemption is required to ensure the continued availability of tests produced in public-sector laboratories that are not suitable for CE marking:

- Rare Disease testing
- Customized tests for common genetic diseases
- Cytogenetic and other whole-genome testing
- Seldom-used tests for common analytes
- Rapid response to changes in test requirements
- Population-specific tests and test panels
- The safety provided by alternatives in test methodology

What kinds of laboratory/institution should be allowed to avail of the exemption, to achieve this objective?

The exemption should continue to apply only to public-sector health institution laboratories. Such laboratories come under the regulatory supervision of the national authorities, which is a Member State competence.

What kinds of device should be included in the exemption, to achieve the objective above?

Only devices genuinely “manufactured” by the laboratory claiming exemption?

Or everything including commercially-produced multiplex devices labelled “for research use only”, which the laboratory claiming the exemption has validated for diagnostic use?

The current freedom to take unmodified commercial kits labelled “for research use only” and validate them for diagnostic use poses a danger to patients, as the constituent parts of the kit (probes etc.) may change without the manufacturer notifying the kit user. We believe, therefore, that the definition of “manufactured” should be more restrictive.

How would “manufactured” be defined to restrict the exemption to devices which are truly manufactured in-house?

We submit this suggested definition of “manufactured” for the purposes of the in-house exemption:

“Manufactured” means designed and assembled from its component parts or reagents and validated for clinical use, all in the same legal entity.

“Designed” in this context would be defined to include selecting a device or assay from a published method as being suitable for a particular application.

Should Health Institutions be allowed to transfer exempted devices to another legal entity, or to remote locations within a legal entity?

Currently, the in-house exemption only applies when a device is manufactured and used “on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity”.

The current legislation has caused some difficulties for national reference laboratories who may have developed reagents to improve quality (FISH probes, reference materials, etc.) that they wish to distribute to a network of public service laboratories (the UK Health Protection Authority network, for example). Here, the definition of legal entity could be phrased to include networks of health institutions with a shared governance structure. The geographic restriction “premises in the immediate vicinity” would then be dropped.

Our proposed definition of a health institution would therefore be:

“A Health Institution is a public body whose primary purpose is the care and/or promotion of public health. Such a body may comprise a single institution at one location or a network of institutions with a shared governance structure.”

Item 2:

Require that all "in-house tests" fulfil the essential requirements of the Directive

98/79/EC, without being subject to a CE marking?

No. This would create a burden of compliance equivalent to that imposed by CE-marking, which is not practical for exempted tests, for the reasons outlined above. We believe that a combination of government oversight of public health institutions and accreditation to an international standard provides an appropriate balance of test availability and patient safety for in-house tests.

Item 3:

Require that all high risk "in-house tests" are excluded from the exemption provided for by article 1(5) of Directive 98/79/EC and then have to fulfil the essential requirements of the Directive 98/79/EC including the involvement of a notified body?

No. This would create a burden of compliance equivalent to that imposed by CE-marking, which is not practical for exempted tests, for the reasons outlined above. Many of the most important rare disease tests, especially presymptomatic tests, may fall into the high-risk category. Excluding them from the exemption would result in them becoming unavailable and could pose a substantial risk to families with rare diseases. "Protecting" patients by excluding some tests from the exemption may therefore have the opposite effect, placing them at risk because no test is available.

Likewise, newly emerging infectious agents may pose a significant risk to the population. It is of utmost importance that specific tests are being developed in a timely manner in order to monitor and control spreading of the agent. Any delay in the development of such in-house tests by competent specialist laboratories would, therefore, bear a higher risk than a non-CE-marked test developed in an accredited laboratory.

Item 4:

Submit the health institutions and premises referred to in Article 1(5) of Directive 98/79/EC that manufacture "in house tests" to accreditation, based on ISO 15189, or equivalent regulation at national level?

Yes. We believe that restriction of the exemption to health institution laboratories which are properly accredited to EN ISO 15189 or equivalent represents the appropriate balance of oversight, patient safety and test availability. EN ISO 15189 contains the requirement "If in-house procedures are used, they shall be appropriately validated for their intended use and fully documented" and specifies that "The validations shall be as extensive as are necessary to meet the needs in the given application or field of application".

These requirements protect patient safety by ensuring tests are appropriately validated, while maintaining a proportionality by linking the extent of the validation to the intended use.

If, as we propose, this option is adopted, the terms "accreditation" and "equivalent regulation" should be clearly defined to ensure consistency across the EU. The ISO definition of accreditation is

“The procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks” . “

Equivalent regulation” is defined in the OECD Guidelines for Quality Assurance in Molecular Genetic Testing: *“Equivalent recognition should include assessment of competence in services provided, including technical competence and relevant specialist education and training; also compliance with relevant legal, professional and quality management standards”*.⁵ This should be clearly distinguished from certification or licensing.

Question 9:

If the exemption provided for by article 1(5) of Directive 98/79/EC should not be maintained, would you consider it necessary to exempt in vitro diagnostic medical devices intended for diagnosis and monitoring of diseases or conditions affecting not more than 5 in 10,000 persons in the European Union from the scope of the IVD Directive and, if yes, why?

No. We do not believe that an exemption for rare diseases would be in the interests of patients. Our alternative proposal, that the exemption for all in-house tests should be retained but restricted to health institution laboratories accredited to EN ISO 15189 or equivalent (see answer to Question 8 and Item 4 above), provides for the availability of testing for rare diseases through Centres of Expertise as envisaged in the Council of The European Union Recommendation on action in the field of rare diseases of June, 2009.

A blanket exemption for tests for Rare Diseases would not achieve the desired aims for several reasons:

1. People with rare diseases deserve the same protection from harm as those with more common diseases. The regulatory framework should be flexible enough to give assurance of the quality and reliability of all IVDs, however rare or common the diseases for which they are used. Retention of the in-house exemption, restricted as suggested above, provides this flexibility while assuring the quality of tests for rare diseases.
2. Diseases which are rare at EU level may be common in some member states or regions, so any cut-off chosen for exemption from the scope of the Directive would be arbitrary and potentially discriminatory.
3. Such an exemption would permit the marketing of test kits for rare diseases without any regulatory oversight to ensure their quality, suitability or effectiveness. These kits could be used by laboratories not expert in their use and not expert in the interpretation of the results obtained, an entirely undesirable situation for those with rare diseases and their families. The only “level playing field” with which we should be concerned is a level playing field for all patients and their families.
4. A combination of the abolition of the exemption for in-house tests and the creation of a new exemption for tests for rare diseases would not address the availability of other types of specialized tests for which no CE-marked IVD will ever be available; rarely-used and

specialised testing is not restricted to rare diseases, as illustrated in our responses to question 7 above.

Question 10:

Do you see a need for a clarification of the scope of Directive 98/79/EC to make clear that it covers all genetic tests that have a direct or indirect medical purpose while clarifying that tests without any direct or indirect medical purpose remain outside the scope of the Directive 98/79/EC?

It would be useful to clarify that (for example) presymptomatic and prenatal tests for conditions which have not yet manifested are included in the scope of the Directive. These tests may have far-reaching implications for subjects and their families.

However, not all such tests are genetic tests.

Item 1:

**Extend the scope to all genetic tests by adding a specific indent in the definition of in vitro diagnostic medical devices regarding devices which pursue the purpose of providing information concerning “results obtained by analysis of the genome”
Should, in this case, an exclusion be introduced in the Directive 98/79/EC as regards some categories of tests (negative list) e.g. paternity, DNA comparison?**

Not all presymptomatic tests require analysis of the genome; some may be based on analysis of RNA, protein or other (combinations of) biomarkers. The suggested wording could leave the status of such tests unclear. We prefer the option below as it focuses on the purpose of the tests rather than the analyte.

Whilst some DNA tests, such as forensic and paternity tests, clearly fall outside the IVD Directive, nutrigenetic tests, which are intended to improve health and prevent disease, and which often give risk predictions for common diseases such as cancer and heart disease, should be considered IVD devices.

Item 2:

Clarify that tests, including genetic tests, with a direct or indirect medical purpose are included within the scope of Directive 98/79/EC.

This option is preferable to Item 1, although it would need to be clarified by definition of “direct” and “indirect medical purpose”

The uncertainty in this area seems to be centred around tests with a (claimed) predictive value. A third option, therefore, would be simply to add “prediction” to the definition of a medical device in Article 1(2)(a) viz:

(a) 'medical device` means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prognosis, prevention, monitoring, treatment, **prediction** or alleviation of disease,

Question 11:

Do you see a need to create **additional requirements or restrictions for direct-to-consumer genetic tests** in order to ensure a better level of health protection? If yes, on which aspects?

The need for action

The direct-to-consumer (DTC) genetic testing market is one where there are profound asymmetries of information between companies and consumers arising from both the novelty and the complexity of the science. There is significant potential for harm due to the vulnerability of consumers - the public may be misled by promotional hype since they lack the scientific knowledge to assess the veracity of companies' claims.

A number of academic studies have looked at the websites of DTC genetics companies and identified problems with the quality of information provision. Geransar and Einsiedel sampled 24 companies and found that background information on diseases tested was "not always complete, pertinent, or accurate".⁶ Sterling's review of 82 nutrigenomic services concluded that their websites "failed to provide adequate and transparent information for informed decision-making, for instance, only 20% informed consumers whether testing was carried out in a certified laboratory and only 11% provided information regarding the analytical or clinical validity of tests."⁷ Hennen et al undertook a review of 38 companies offering genetic tests DTC, assessing the quality of information provision using 12 criteria established by Datta et al.⁸ They found that 55% of companies (21 out of 38) complied with four or fewer of the 12 criteria, and concluded that such "fundamental information deficits [had] ... possibly far-reaching consequences for consumers."⁹

There have been longstanding concerns about the quality of the science underpinning consumer genetic tests and the most recent reviews of the scientific validity of the tests concluded that: 1) there was insufficient evidence to support the claims made by many of the companies¹⁰; and 2) even amongst those companies who restrict themselves to reporting on well-validated gene-disease associations there are major discrepancies, with the same the individual receiving different risk information depending on which genes are being tested for.¹¹ Furthermore, the field is moving so quickly that a person's risk profile may change from high to low risk and back again as new gene-disease associations are discovered.¹² Thus, experts interviewed for the US Government Accountability Office's recent report considered that our scientific understand of the genetics of common, complex diseases is still too limited for such tests to be of clinical use.¹³

These concerns relate to the mainstay of the DTC genetics market: testing for susceptibility to common diseases. However, there is a trend towards some companies offering more traditional clinical genetic tests to consumers, reporting on a range of monogenic disorders such as cystic fibrosis. Here the concern is not the lack of clinical validation, since these are well-established genetic tests, but the lack of medical supervision and pre- and post-test counselling. There is widespread international support for the view that such genetic tests should be offered only in the context of medical supervision and with appropriate genetic counselling. This principle is central to the OECD guidelines on quality assurance for molecular genetic testing which have the support of all OECD member states.

Whilst the concerns about susceptibility testing focus both on the quality of the tests, and misleading claims, the concerns about DTC provision of testing for monogenic disorders focus mainly on the quality of the service. How might one respond to these different concerns? Broadly speaking there are four possible responses to the DTC genetic testing market:

- 1) A complete ban (i.e. either making all genetic tests prescription-only, or making all IVD devices prescription-only)
- 2) Restrictions on some tests or some forms of service delivery (e.g. classifying some tests prescription-only)
- 3) Subjecting tests to the normal requirements of the medical device regulations (including special regulations governing devices intended for use by consumers)
- 4) Reliance on soft law mechanisms such as a code of practice

Options one to three are probably of greatest relevance to authorities responsible for medical device regulation (although they could also have responsibility for enforcing a code of practice). There are currently examples of option one (Germany and this will be in operation in Australia when their new device regulations pass into law later this year), option four was in force in the UK (but is no longer) and is also in operation in Japan. Option two is probably in operation (in principle at least) in a number of European countries where there are restrictions on who can provide all, or some categories of, genetic tests. In the USA FDA is now considering how it will regulate DTC genetics companies under the FDCA. Their response seems likely to be a combination of options two and three, although FDA is still considering how best to exercise its authority over LDTs, and some adjustment to its traditional regulatory mechanisms might be anticipated.

In the absence of a mechanism for a harmonised approach to the regulation of DTC genetic tests, then some European countries have chosen to take unilateral action. However, other member states have taken the view that such unilateral action is incompatible with the single market intent of the IVD Directive. We believe that the Directive should be revised in order to address the problems arising from DTC genetic tests on an EU-wide basis. Concerns about the quality of service and lack of medical supervision should be addressed by identifying those tests which may be made available on a direct-to-consumer basis and those which may only be provided with medical supervision. This should be done not only for genetic tests but all IVD devices. Direct-to-consumer advertising of tests which are classified as prescription-only should be illegal.

We believe that the following classes of genetic tests should *without exception* be classed as prescription-only:

1. Diagnostic tests	Tests intended to diagnose a medical condition in a person with symptoms and/or signs.
2. Pre-symptomatic tests	Tests intended to predict that an asymptomatic person has a high probability of developing a condition, for example, BRCA tests for breast cancer and mutation testing in some autosomal dominant single – gene disorders, such as Huntington Disease. This is sometimes referred to as predictive testing.
3. Carrier testing	Tests intended to show that a person is a carrier of a condition, so that although they are not themselves affected, there is a risk

	they may have affected children.
4. Prenatal diagnostic tests	Tests intended to identify medical information about a fetus or to establish fetal sex.
5. Pharmacogenetic tests	Tests used to predict the response profile of an individual to a drug or other course of therapy.

We believe that *in some cases* tests from the following classes could be made available DTC:

6. Susceptibility/predisposition tests	Tests intended to predict the absolute lifetime risk or relative risk of an individual developing a condition where the probability is relatively low compared with the types of risks identified by pre-symptomatic tests.
7. Nutrigenetic tests	Tests used to provide information about how an individual responds to a particular nutrient or diet

However, we believe that susceptibility tests for serious or potentially fatal diseases should not be available DTC - e.g. cancer, stroke - particularly where the test may cause undue anxiety or may result in serious preventive measures (e.g. prophylactic surgery in case of cancer). Furthermore, with regard to nutrigenetic tests, any claims which could be classed as disease risk should lead to classification of the test as a susceptibility test.

For those tests where DTC provision is permitted then rule 4 of the GHTF risk-classification model should be followed in order that concerns about the quality of the tests are addressed by subjecting them to pre-market review in order to ensure truth-in-labelling and truth-in-promotion. However, it should be noted that since DTC genetic tests are all laboratory-developed tests (LDTs), then addressing this market requires clarification of the scope of the Directive in relation to LDTs produced in commercial laboratories.

Ensuring truth-in-labelling is a fundamental aspect of the Directive's purpose. Yet there is currently no regulatory equivalent of a product label for LDTs. Although a significant move in this direction has been made in the United States as a result of a recent FDA guidance, in Europe it is not clear how the concept of truth-in-labelling should apply to LDTs.¹⁴ Since the Directive covers promotional material as well as product labels, then the information which laboratories make available to doctors and patients in printed materials and on their websites, would be covered by the Directive. However, in the case of promotional material it is the manufacturer who decides which types of information to provide to the user; whereas with the product label, the Directive clearly sets out requirements about which types of information *must* be provided to the user, and it is therefore a much more powerful regulatory tool for ensuring comprehensive, easily understood and accurate information. Guidance is required on how to apply these requirements to LDTs.

The regulation of these tests becomes more complex because of some of the complex chains of supply which can be involved. We can illustrate this with a real-world example which involves three companies: a manufacturer, a laboratory and a company with a clinical interpretation service.

Roche Molecular manufactures the Roche Amplichip, a pharmacogenetic microarray which identifies CYP450 genes. Roche supply the test to LabCorp, a leading reference laboratory in the US. LabCorp send test results to a Canadian company called Seryx, who use a computer database of clinical data and an interpretative algorithm to provide clinical interpretations of the test results. They send their

clinical interpretation back to LabCorp who then pass this on to the ordering physician. FDA have stated that Seryx’s algorithm is a medical device and subject to their regulations but would these companies be subject to the Directive?¹⁵

Roche Amplichip ⇨	LabCorp ⇨	⇨ Seryx Signature Genetics
Roche supply test kit to labs	Labs perform the test and send results to Seryx	Seryx provide labs with clinical interpretation of test results using a database of clinical data and computer algorithm

The market for genomic tests increasingly involves reference laboratories (or companies providing interpretative services) located outside the European Union. This includes both DTC companies and others who do not offer their tests DTC but partner with a European firm who take patient samples and report the results to the patient e.g. the US company Genomic Health is offering its Oncotype Dx test in Europe through a partnership with Medical Solutions, a UK firm.

The advice we have received from both the MHRA and the European Commission suggests that in neither case would the tests provided by companies outside the EU be subject to the IVD Directive. It would appear that in the UK at least, the regulatory status of Oncotype Dx and other LDTs which are sold in the EU, but where the test is conducted in a country outside the EU would seem to rest on the question of whether what is being sold is a product or a service. It seems that those physical elements of the test which are present on EU territory, e.g. the kit for collecting the sample, have been classed as IVD devices and the manufacturer is obliged to CE mark the products. Those elements of the test which are not physically present on EU territory are classed as not falling under the IVD Directive – these elements would include the kit to test the sample, the algorithm which provides the risk score etc. Yet since they are integral to the test, and the test is being sold to EU citizens, then all these elements have been ‘put onto the market’ within the EU. Furthermore, since the IVD Directive treats LDTs as medical devices, then one cannot justify exempting these aspects of the test on the grounds that an LDT is a service rather than a product. For the purposes of the IVD Directive an LDT may be a service but it is also a product, in this case a medical device. It therefore follows that those who sell LDTs to EU consumers are selling medical device products in the EU, even if those products are also services performed outside the EU. To put the contrary argument, that the test is a service performed outside the EU and therefore not subject to the Directive, is to argue that a test cannot be a service and a product.

Furthermore, whilst there is no explicit reference in the Directive to such arrangements which would clearly cover such tests, we are not aware of any provisions within the Directive which clearly indicate that such tests are not covered by the Directive. We would suggest that since the Directive clearly covers commercial LDTs, then there is no reason to exclude these tests and that to do so would not only be a failure to protect public health but would also provide a perverse incentive for EU companies to locate their operation outside the EU, an outcome incompatible with the objective of the Commission’s Life Sciences and Biotechnology Strategy which commits it to supporting the development of the European biotech sector.

The essential requirements of Directive 98/79/EC foresee requirements regarding the performances of *in vitro* diagnostic medical devices. In particular, the **demonstration of performance** should include, where appropriate analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection,

stated by the manufacturer. These requirements are a mix of analytical and clinical requirements.

Question 15:

Do you see a need to **further clarify the requirements regarding clinical evidence** for *in vitro* diagnostic medical devices?

Yes.

4.1 Clinical validity

The **clinical validity** is the demonstration of the performance characteristics supporting the **intended use** of the *in vitro* diagnostic medical devices and includes diagnostic sensitivity, diagnostic specificity based on the true disease status of the patient and negative and positive predictive values based on the prevalence of the disease. These two last elements (negative and positive predictive values based on the prevalence of the disease) are currently not clearly mentioned in the Directive 98/79/EC.

Question 16:

On the basis of the above, do you see a need **to extend the requirements** regarding the demonstration **of the clinical validity** in Directive 98/79/EC?

We believe that it should be mandatory for manufacturers to state the test's intended clinical purpose and to provide data on both analytic and clinical validity (although for clinical validity it may be sufficient to cite the existing scientific literature). When we presented these ideas to the Competent Authorities at their 2007 meeting in Lisbon it became apparent that there is significant disagreement between member states on this issue, with some taking a similar view to us and others taking the view that the Directive only requires data on analytic validity. Disagreement on such a fundamental point is a serious cause for concern. Neither public health nor industry are well served by such a lack of clarity.

Our research would suggest that most stakeholders believe that the Directive requires manufacturers to provide evidence of a test's analytic validity, but only requires evidence of a test's clinical validity if clinical claims are made by the manufacturer. An international comparison indicates divergence between the US and Canadian systems and those of the European Union and Australia in this regard.

Country/region	Analytic validity	Clinical validity
USA	Yes	Yes
Canada	Yes	Yes
Europe	Yes	Only if clinical claims made?
Australia	Yes	Only if clinical claims made?

However, there are a number of reasons to believe the common interpretation of the IVD Directive may be wrong, and that to fulfil the requirement of the Directive requires data on clinical validity:

1. Guidance on Research Use Only products states that IVD devices must have a clinical purpose.
2. You cannot classify risk without a clinical purpose.

3. You cannot fulfil Essential Requirements one and three without a clinical purpose and data on clinical validity

1. Can you distinguish between research use and clinical use without an intended clinical use?

MEDDEV guidance issued in 2004 on research use only products highlights the issue of the distinction between research and clinical use. This guidance clearly states that an IVD test with no intended medical purpose is not a test under the IVD Directive, it is simply an RUO product.

“In summary for a product to be categorized as an RUO product it must have no intended medical purpose or objective ...When a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.”¹⁶

Since the guidance states that the manufacturer must define the device’s medical (or clinical) purpose, then they must make a clinical claim, and if they make a clinical claim then they must support it with evidence.

2. Can you do risk classification without an intended clinical use?

Returning to the previous issue of classifying a test as higher risk, we might ask how points i) and ii) in the list of criteria which determine if a test might be added to Annex II can be considered in the absence of a specific clinical use. For instance, point i) requires one to consider “whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action”. Since as noted above, risk-based classification is central to the Directive’s approach to regulation, then anyone who sets out to answer these questions can only do so in relation to a specific intended clinical use. Again, once a manufacturer has a stated clinical purpose for a test, then they must provide data on its clinical validity.

3. Can you fulfil the Directive’s essential requirements without an intended clinical use?

Finally we can turn to the Directive’s essential requirements concerning safety, quality and performance which all IVDs must comply with before being CE marked and placed on the market. Is it possible to fulfil the Directive’s essential requirements by only providing data on a test’s analytic validity? GR Higson, a UK expert on device regulation closely involved in the development of the medical devices directives, commented on this issue, stating that:

final confirmation of the safety and performance of a medical device is normally provided by observation of the behaviour of the device in its intended use with patients ... Essential requirements 1 and 6, and in some cases 3, can only be satisfied by the evaluation of clinical data relating to the use of the device.¹⁷

The first essential requirement states that the test must not “compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons”. Furthermore, any risks conferred by the test must be outweighed by the benefits to the patient. Common sense suggests that one can only assess the benefits of a device in relation to an intended clinical purpose.

Risk assessment also requires a clinical purpose for the device. Manufacturers must assess “any indirect risks which may be associated with their use”. For IVD devices the main indirect risks are the clinical consequences of an incorrect result. Since such false results might arise from either poor

analytic validity or poor clinical validity, then comprehensive risk assessment must evaluate the clinical validity of the test in its intended use.

As noted in the consultation document, the most relevant part of the Directive is the third essential requirement. Requirement three states that devices must meet the manufacturer's specifications, taking into account "the generally acknowledged state of the art". Performance criteria that may be appropriate include "analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity". Common usage of these terms would lead one to understand analytical sensitivity and specificity as referring to analytic validity and diagnostic sensitivity and diagnostic specificity as referring to clinical validity.

Finally, it should be noted that clinical validity does not relate only to "true disease status" - in connection with predictive testing it is "future disease status" and in relation to companion diagnostics it is "treatment response".

4.2 Clinical utility

Beside the notion of clinical validity, the notion of **clinical utility** is the demonstration of the potential usefulness and added value to patient management decision-making. The notion of clinical utility for the purpose of this document **does not include cost/benefit assessment, reimbursement issues and/or health economics issues**. If a test has a utility, it means that the results provide valuable information for the purpose of making decisions about effective treatment or preventive strategies.

Question 17:

In the context of the above, do you see a need to **require the demonstration of the clinical utility** of the parameter in Directive 98/79/EC? If yes, how should the clinical utility be demonstrated?

Our research found broad support for the view that data on analytic and clinical validity are minimum data requirements but that it is both generally unrealistic to ask statutory regulators to evaluate the clinical utility of tests, and probably constitutes too high a barrier to market entry. Reviewing evidence on utility is more appropriately done after tests have entered the market, and handled by other gatekeepers, for instance through HTA mechanisms at the level of resource allocation and through clinical practice guidelines. Such a model fits well for those companies who make claims about only the analytic and clinical validity of their tests; however, it may be that companies wish to make claims about the utility of their tests (this seems particularly likely in relation to pharmacogenetics where a test used to guide treatment selection). Since those responsible for the regulation of medical devices have a duty to ensure both truth-in-labelling and truth-in-promotion, then it seems logical that, when companies choose to make such claims, then evidence to support any such claims should form part of the technical file and be reviewed as part of pre-market evaluation of the test.

Question 18

Would you consider the possibility of a **conditional CE marking** in certain situations useful? Which situations would you think of and which conditions, including procedural requirements, would you consider necessary?

Pre-market review of the analytic and clinical validity of tests have been recommended here as the minimum common requirements for genetic/genomic tests, but this cannot provide sufficient protection in all cases. Where a test is considered higher risk because of its intended clinical use or

the novelty of the technology, and has only limited data to support its use, it may be appropriate to delay market approval pending further studies. However, even here there may be ways to minimize the regulatory burden. One option is to allow a more controlled entry to the market by using conditional approval or mandated Phase IV studies. Use of this mechanism may be favoured where a new test is deemed high-risk but promises to meet an urgent clinical need and/or where the manufacturer has already gone some way to developing a convincing evidence base.

Procedural requirements might vary from a statement that post-marketing data be collated and presented for review a set period after first marketing, or a more directive approach which lays out in some detail the evidentiary requirements, in terms of scale of study, population etc. It needs to be considered who should be responsible for setting such requirements and whether it is really appropriate for a Notified Body to have such power, or realistic to expect them to wield it.

Question 19:

Which options do you see to guarantee a high quality of IVD medical devices used as companion diagnostics?

EMA has a particular interest in pharmacogenetics, but its current lack of authority over diagnostic tests means that whilst it can authorise a new medicine whose prescription requires the use of a pharmacogenetic test, it cannot authorise the diagnostic (Hogarth et al, 2006). The safety and effectiveness of drugs tied to a companion diagnostic is heavily dependent on the analytic and clinical validity of the companion test. There have been notable problems with companion diagnostics, in particular long-running issues regarding the accuracy of Her-2 testing.¹⁸ We believe that the development of pharmacogenetics is hampered by EMA's lack of authority and giving EMEA authority over pharmacogenetic tests is a necessity for the consistent and comprehensive regulation of this emerging area

N.B. We stated in our response to the broader recast consultation that a role for EMA in relation to higher risk devices would be one way to address well-documented shortcomings with the system of Notified Bodies. We are not restating our position on EMA's possible broader role here, as it is not within the bounds of the current questionnaire; however our opinion on the subject remains the same.

Contacts

All enquiries relating to this document should be directed to

Professor David Barton

National Centre for Medical Genetics, Dublin, Ireland

Tel: +3531 409 6749

david.barton@olchc.ie

or

Dr Stuart Hogarth

Global Biopolitics Research Group

Department of Political Economy

King's College London, UK

Tel: +44 (0)20 7848 1802

stuart.hogarth@kcl.ac.uk

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