Official response of the Dutch Society of Clinical Genetic Diagnostic Laboratories (Vereniging Klinisch Genetische Laboratoriumdiagnostiek; VKGL)

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

VKGL is the Dutch society for clinical genetic laboratories, including molecular, cytogenetic and biochemical laboratories. All member laboratories are accredited in compliance with the standard ISO15189 “Medical laboratories — Particular requirements for quality and competence”. The member labs are the only laboratories in The Netherlands licensed to perform clinical genetic laboratory investigations.

Main points of view of the VKGL:

- 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, to which our members actively contribute, ensures the availability of safe, effective, appropriate, and patient-oriented genetic testing. Furthermore, we fully agree with the statement in the OECD Guidelines for Quality Assurance in Molecular Genetic Testing: “All molecular genetic testing results for clinical care purposes should be reported by competent laboratories, as established by accreditation or other equivalent recognition”.
- 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. Without such tests, the practice of medicine that we know today would be severely reduced in scope.

VKGL 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 have restricted our responses to questions 7 to 11 concerning the in house exemption, the scope of the Directive in covering some genetic testing, and direct to consumer (DTC) products/services, as these issues are within the area of concern of the VKGL.

This response has been formulated following discussions with scientists in VKGL member laboratories, Eurogentest, and the European Society of Human Genetics. This response does not represent the views of particular individuals or organizations, but is a reflection of their general vision on these matters.
We wish to acknowledge the following scientists with whom the following items have been discussed extensively:
Prof. David Barton, Chief Scientist & Associate Professor National Centre for Medical Genetics, Dublin, Ireland, also acting on behalf of Eurogentest
Dr. Layla Theiner, Public Affairs Manager, Cancer Research UK

If you have any questions on this response, please contact Hans Scheffer, chairman VKGL, associate professor clinical molecular genetics, head Division DNA Diagnostics, Dept. Human Genetics, Radboud University Nijmegen Medical Centre, The Netherlands (h.scheffer@antrg.umcn.nl)

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 needs clarification 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, fragile X syndrome), 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 impossible. 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.

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. Whole-genome testing including cytogenetics
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.
The exemption for in-house tests ensures their availability.

6. 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.

7. 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.

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. 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?

Yes, it will be essential to provide clear definitions, as these will determine the scope of the exemption.
The exemption is required to ensure the continued availability of tests produced in public-sector laboratories that are not suitable for CE-marking, as mentioned in answer 7.
The exemption should continue to apply only to public-sector health institution laboratories. Such laboratories come under the regulatory supervision of the national authorities.

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 (including the selection of a device or assay from a published method as being suitable for a particular application) and assembled from its component parts or reagents and validated for clinical use, all in the same legal entity.

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.
A definition of a health institution could 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.

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 ISO 15189 or equivalent represents the appropriate balance of oversight, patient safety and test availability. 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. Availability of recognized competent professional expertise in the accredited labs is crucial. This has been defined in the OECD Guidelines for Quality Assurance in Molecular Genetic Testing: “(..) 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”.

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 limiting the exemption to rare diseases alone 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.

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

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, is suggested by Eurogentest. VKGL supports this suggestion: add “prediction” to the definition of a medical device in Article 1(2)(a).

(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, 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?

In the direct-to-consumer (DTC) genetic testing market in many instances insufficient information is provided by the company to the consumer. This is in part due to the lack of sufficient clinical validation. These concerns relate to the mainstay of the DTC genetics market: testing for susceptibility to common diseases. However, there is also 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.

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. Scientific evidence for the utility of such tests must be available.
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.