Europe to ban direct-to-consumer genetic tests?

To the editor:

In the February issue, Charles Schmidt[1] describes some of the regulatory challenges associated with the boom in direct-to-consumer genetic tests marketed by companies in the United States and Iceland. On May 7, the Committee of Ministers of the Council of Europe approved an additional protocol concerning genetic testing for health purposes[2] to the Convention on Human Rights and Biomedicine. This additional protocol deals partly with direct-to-consumer services and as such has the potential to directly affect the business of companies providing direct-to-consumer genetic testing in Europe.

Article 7.1 of the protocol states that "a genetic test for health purposes may only be performed under individualized medical supervision." In the Council's explanatory report[3], the premise for the amendment to the Convention is laid out: Article 7.1 has been "driven by the concern to enable the person concerned to have suitable preliminary information with a view to an informed decision regarding the carrying out of this test and, if appropriate, to have access to appropriate genetic counseling. A precise evaluation of the situation of the person concerned, involving direct contact with him or her, is a determining element in that respect. A mere telephone conversation with a medical doctor, for example, does not allow for such evaluation"[3].

The Council of Europe's deliberations were preceded by several nonbinding documents and advisory reports on genetic testing from groups in European member states, including the UK's Human Genetics Committee[4], the Belgian Advisory Committee on Bioethics[5] and the National Consultative Ethics Committee for Health and Life Sciences in France[6]; a report commissioned by the Portuguese government is also expected shortly. Concerns about oversight of genetic testing were also raised by the European Group on Ethics in Science and New Technologies—a neutral, independent, pluralist and multidisciplinary body appointed by the European Commission (Brussels) to examine ethical questions arising from science and new technologies. In its 2003 statement, it pointed out "several serious problems in ethical, social and legal terms," raised by the marketing of genetic tests directly to the public[7]. And earlier this year, the European Society of Human Genetics announced that it is preparing a policy document on this topic[8]. The published reports all criticize the lack of a coherent regulatory landscape in Europe.

If the European Council's proposed restriction is enacted in the various European member states, direct-to-consumer services, such as those currently offered by genetic testing companies, could effectively be prohibited in Europe. The big 'if', however, is whether European member states sign up to the protocol. In the past, countries such as the United Kingdom and Germany have neither signed nor ratified the European Convention (or its additional protocols); to date, of the 46 member states of the Council of Europe, a total of only 34 and 21 states have signed and ratified the original Convention, respectively. The date of the opening for signature for the most recent additional protocol is expected to be this November. This means that several years may pass before the additional protocol enters into force, and it will apply only in those countries that have ratified it.

In addition, discussion might arise about what is being regulated by this additional protocol. According to the scope of this protocol, it should apply "to tests, which are carried out for health purposes, involving analysis of biological samples of human origin and aiming specifically to identify the genetic characteristics of a person which are inherited or acquired during early prenatal development (hereinafter referred to as "genetic tests")." However, some direct-to-consumer companies make a distinction between making claims that directly affect healthcare decision making (which might fall under the additional protocol) and making health-related claims (which does not fall under the additional protocol). For example, the genome scanning company 23andMe (http://www.23andme.com) argues that the "genetic information provided…about potential health conditions should not be used to estimate your overall risk of future disease" and that it is not "intended to be medical advice."

One other legislative mechanism that may affect direct-to-consumer tests is the *In Vitro* Medical Devices Directive 98/79/EC (IVD directive)[9]. The purpose of this Directive is to ensure that safe and functional products are sold within the European market. It regulates, among others, the free movement of 'CE marked' goods in the European Union, conformity assessment procedures, risk assessment and vigilance. Genetic tests are considered to be regulated by this IVD directive, but the current pre-market evaluation mechanisms do not sufficiently apply to genetic tests. Stuart Hogarth and David Melzer have identified various sources of ambiguity with regard to the European regulation of genetic tests and made an appeal to enhance the regulatory framework[10]. In May, the competent authorities launched a public consultation on the IVD Directive with the view to revise the directive. The Science and Technology Options Assesment, an official organ of the European Parliaments, has also commissioned a project to explore the use of direct-to-consumer test services[11]. It seems likely that any revision of the IVD Directive might affect much more heavily the regulation of genetic tests and direct-to-consumer genetic tests in particular.

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Dichotomies between computational and mathematical models

To the editor:

In a timely review in the November issue entitled "Executable cell biology," Jasmin Fisher and Thomas Henzinger[1] couple descriptions of new computational approaches for cell biology science with a vision of an emerging, new field. Although we are in full agreement with their basic message and vision, the review lacks clarity on several key points that may confuse skeptical readers, prospective new students and future practitioners of this emerging field. Below, we share several observations intended to strengthen the message and clarify the original vision outlined in the review.

On page 1240, Fisher and Henzinger state, "Whereas an algorithm must be devised to simulate a mathematical model, a computational model prescribes the steps taken by an abstract machine and is therefore inherently and immediately executable. As the primary semantics of computational models are operational, we use the term execution instead of simulation—hence executable biology." Technically, both mathematical and 'computational' models used in biomedical research prescribe steps to be taken by an abstract machine. Algorithms must be devised to execute either model type. Traditional mathematics, Statecharts and Reactive Modules are all specification languages in the same general category. They are formalisms. A model written using a formalism is translated into a computer program, which is then executed by a computer. That sequence is true for both mathematical and computational models.

Thus, by claiming mathematical and computational models are differentiated by their formalisms, Fisher and Henzinger draw a false dichotomy between the two model classes, one that some readers may see as a theme of this review. The important difference between the two model classes is not in the formalisms. It is in (i) the intent and approach used by the scientist, (ii) what the computer is doing when implementations of those models are executed and (iii) why the computer behaves as it does. Both model classes are usage oriented. When a model of the type described in Box 3 of the review has been applied to biology, the result has most often been an analog device or mechanism rendered in software. The traditional use of mathematical models in biology has been to describe data: when the implementation of a mathematical model is executed, values may be generated that closely match the original data. In contrast, during execution, the mechanisms of an analog device actually function in ways that are thought to mimic a biological mechanism at some level of abstraction.

Both model types must be translated from the formalism into machine code. The authors' rhetoric hinges on an implicit assumption: that the translation between computational models and machine code is more automated than the translation between mathematical models and machine code. The existence of Mathematica, Matlab and symbolic math tools is the evidence that this assumption is false.

In the next paragraph, the authors build on this false dichotomy. "Because computational models are qualitative, they do not presuppose a precision absent from the experimental data; because they are nondeterministic or stochastic, they allow many possible outcomes of a chain of events, which is often observed in biological systems." But in reality, computational models are just as quantitative as mathematical models. Part of the problem is their implicit assumption that 'quantitative' is identical to a continuum (or mathematical metric space). Except in the case of hybrid systems mathematics, it is true that mathematical models usually assume a continuum. In contrast, it is also true that computational models often operate in or on less well-formed data (e.g., measures as opposed to metrics and nonmetrizable sets as opposed to metric spaces). Nevertheless, digital computer software must still be crisply specified because when implemented it tolerates no ambiguity in its values; thus, computational models, when translated into machine code and executed, are just as quantitative as mathematical models.

Moving to Box 3 of the review, under "Boolean networks," we disagree with the statement that all computational models are stochastic or nondeterministic, as expressed by the authors. For example, chaotic models (deterministic and nonstochastic, yet unpredictable) are also possible using computational formalisms (e.g., those in Box 3). Of course, mathematical models can also be nondeterministic, stochastic or chaotic, but the task of making them so can become complicated.

In the section "Quantitative versus qualitative modeling of biology," the authors write, "A significant advantage of qualitative models is that different models can be used to describe the same system at different levels of detail and that the various levels can be related formally." By not pointing out that the same can be said of mathematical models, the authors imply that traditional mathematical models cannot be used to describe the same system at different levels of detail and/or that the various levels cannot be related formally. It would be incorrect to draw that inference, as mathematical models can be hierarchical, and a multi-level mathematical model can contain variables at one level that are mechanisms at another. Hence, by making their statement without an equivalent one about traditional mathematical models, the authors reinforce the false dichotomy.

The next section begins: "Computational models can be analyzed by model checking. Computational models can be used for